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THE ROLE OF THE ENDOGENOUS OPIOID SYSTEM IN THERMOREGULATION DURING EXERCISE

by

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INDEX

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Whatever you do, work at it with all your heart,
as working for the Lord not for men....

Colossians 3:23

I wish to dedicate this work to the Lord Jesus Christ whom I recognise as my personal Lord and Saviour.

My sincere thanks to my wife Riana for her love, support and encouragement.

A special thanks to my parents for their support of my academic career.

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Martin P Schwellnus

August 1988

DECLARATION

I, M P Schwellnus declare that the work on which this thesis is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part thereof has been, is being, or is to be submitted for another degree at this or any other University.

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ABSTRACT

In man the metabolic heat produced during physical exercise stresses the thermoregulatory system, particularly if hot, humid environmental conditions prevail. It has recently been postulated that endogenous opioids may play a role in regulating body temperature at rest and because it has also been shown that blood levels of these substances increase during exercise, the possibility exists that endogenous opioids may play a role in thermoregulation during exercise. A study was conducted in two parts to determine the thermoregulatory response during exercise with and without pharmacologic blockade of the opioid receptor. In Part I nine healthy male subjects perfomed 30 minutes cycling at 50 % maximal aerobic capacity in an environmentally controlled laboratory. The subjects received either placebo, 2mg or 10mg naloxone hydrochloride in a randomized double blind crossover fashion prior to the exercise test. Rectal temperatures were recorded at one minute intervals and cardiorespiratory parameters were measured during the test. Water loss was calculated from differences in nude body weight.

In part II eight male subjects performed a graded maximal cycle ergometer test after receiving either placebo or 2mg naloxone in a randomized double blind crossover fashion. Rectal and sublingual temperatures were recorded before and after the test and oesophageal temperature was recorded at one minute intervals during the test. Cardiorespiratory parameters were recorded during the test.

The results of Part I show that rises in rectal temperature as well as calculated water losses were similar for placebo and after the administration of both 2mg and 10mg naloxone.

Similarly during maximal exercise (Part II) the rise in rectal and oesophageal temperatures was equivalent for placebo and 2mg naloxone but sublingual temperature failed to rise during exercise following the 2mg naloxone dose. Cardiorespiratory responses did not differ between placebo and naloxone tests in both Part I and Part II of the study.

These results indicate that naloxone-mediated blockade of opioid receptors does not affect rectal and oesophageal temperature responses to either submaximal or maximal exercise. Naloxone appears to selectively alter the sublingual temperature response to exercise possibly by altering local blood flow.

It is concluded that insofar as naloxone induced opioid receptor blockade provides a measure of the function of the endogenous opioid system, this study suggests that the endogenous opioid system does not play a significant role in thermoregulation during exercise.

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CHAPTER ONE

INTRODUCTION

The single cell is the functional unit of the human body and each tissue is made up of a vast number of cells. A study of the human cell and tissues reveals that their function is dependent on an amazing number of metabolic processes. Furthermore, these metabolic processes are under the control of enzymes which in turn function only within certain limits of temperature. If the temperature is too high the enzymes are destroyed, while at low temperatures enzymatic reactions are retarded and finally cease.

In man internal (core) temperature is regulated within a very narrow range (Homeotherm). The ability to produce heat when exposed to cold environmental conditions and to dissipate heat when exposed to hot environmental conditions allows man to maintain his core temperature constant despite changes in environmental conditions. This ability regulates the internal cellular environment and results in optimal function of the enzyme systems in man. Circumstances can however arize in which the core temperature regulatory system is stressed as occurs during exposure to extreme heat or cold. Under such conditions specific compensatory responses must take place to ensure that core temperature remains within normal limits. An inadequate response, or even a failure of such compensatory responses can result in cellular dysfunction or necrosis which can lead to the death of the organism.

Physical exertion is an integral part of man's daily occupational and recreational activity. Physical activity is also a stress to the temperature regulatory system. The metabolic heat produced during physical activity stresses the heat dissipating system

particularly in hot, humid environmental conditions. Failure of the mechanisms responsible for heat dissipation can cause severe illness (heat illness) and even death.

The first recorded death presumably as a result of exercise in the heat is a biblical reference (2 Kings 4 : 18-21) recorded in the year 500 BC. This refers to the son of a Shunammite who died a few hours after collapsing while working in the fields (Eichler et al , 1969 ;Shibolet et al , 1976). Numerous other accounts of illness and death presumably as a result of abnormal heat stress, are recorded in history. A Roman historian Dio Cassius (AD 150-235) recorded a disastrous campaign of Aeluis Galluis (24 BC) in Arabia in which a large part of his army apparently died from heat illness. This ultimately lead to their defeat by the Arabian Army (Jarcho , 1967). Heat stroke was not recognized as a seperate clinical entity for centuries and was confused with apoplexy by Forestusin (1562), and by Baglivi (1694). Heat illness also claimed the lives of eleven thousand people in the streets of Peking in July 1743 (Levick , 1858). One of the oldest records of the occurance of heat illness at sea was described by Wellstead in 1841 (Wakefield et al , 1927). On this occasion, thirty crew members and three officers on board a ship sailing from Muscat to Bushire died as a result of heat illness despite efforts to cool them down by wetting the deck of the ship.

Abnormal thermoregulatory function as a result of exposure to heat commonly affected large numbers of unacclimatized people who were exposed to hot, humid environmental conditions during military expeditions (Shibolet et al , 1967), pilgrimages to Mecca (El Halawani , 1964), the gold mining industry (Strydom , 1966) and when working on oil tankers in the Persian Gulf (Leithead , 1958).

Of particular concern in recent years are the reported cases of heat illness occurring in competitive athletes. These occasionally resulted in the death of the athlete. Cases have

been reported in Olympic cyclists, (Shibolet et al , 1976) American football players (Murphy et al , 1965 ; Barcenas et al , 1976 ; Murphy , 1984) and marathon runners (Hanson et al , 1979 ; Aarseth et al , 1986).

Despite the fact that illness as a result of heat stress during exercise has plagued mankind for centuries, the exact mechanisms of causation, predisposing factors, pathophysiology, clinical presentation, management and prognostic features of heat ilness have either been documented only recently or await full elucidation.

The scientific investigation into thermoregulatory function during exercise is marked by a number of historical milestones. These include:
- The observation by Lancisi in 1705 that there is an association between high environmental humidity and heat illness (Wakefield et al , 1927)
- English surgeons and American physicians first recognize heat stroke as a clinical entity in the nineteenth century (Wakefield et al , 1927)
- In 1818 Watts first observed an increased body temperature in heat stroke victims (Eichler et al , 1969)
- In 1859 Levick suggested that lack of heat acclimatisation is a predisposing factor to the development of heat illness (Eichler et al , 1969)
- The American College of Sports Medicine suggest guidelines (American College of Sports Medicine : Policy statement , 1984) to decrease the risk of heat injury during sports participation.

Today much is known about the pathophysiology of temperature regulation during exercise, but research continuously reveals areas where scientific knowledge and understanding is inadequate. The very recent discovery of endogenous opioid neurotransmitters is such a field that requires further investigation (Harber et al , 1984). The precise physiological role of these substances

during exercise has not been elucidated (Copolov et al , 1983). There is some evidence that these substances may play a role in thermoregulatory function during rest in animals (Holaday et al , 1978 (a and b) ; Goldstein et al , 1975) and man (Staessen et al , 1985).

However, very little data are available regarding the role of these substances in thermoregulatory function during exercise. This study was designed to investigate the possible role that endogenous opioids may play in thermoregulatory function during submaximal and maximal exercise. This information is important so that thermoregulation during exercise and the prevention of heat illness might be understood better.

CHAPTER TWO

THE THERMOREGULATORY RESPONSE TO EXERCISE

2.1 INTRODUCTION:

An investigation into the thermoregulatory function of man while performing physical exercise requires a basic understanding of the physiology of heat exchange. In this chapter the following current concepts in thermoregulatory physiology will be discussed:

- Mechanisms of heat exchange

- The thermoregulatory response to exercise

2.2 MECHANISMS OF HEAT EXCHANGE

The accurate control of core body temperature is achieved by balancing heat loss from the body against heat gained by the body (Bell et al , 1980). Heat gain occurs either by increased heat production by the body or by absorption of heat from the

environment (Table 2.1). The following mathematical expression is derived from the law of thermodynamics and describes the heat exchange between the body and the environment.

Body heat balance equation : (Bell et al , 1980 ,p 411)

S = M + E - (+W) + R + C + K where:

S = Rate of storage of body heat (Watts or Watts/m^2)
M = Metabolic production of free energy
E = Heat transfer by evaporation
W = Work against external forces
R = Radiant heat exchange
C = Convective heat exchange
K = Conductive heat exchange

In order for the body core temperature to remain constant at rest or during physical activity the rate of heat storage by the body should approximate zero and this is known as a state of equilibrium (Haymes et al , 1986). During physical exercise only 20 % of the free energy of metabolism appears as external work whilst 80 % is released as heat (Shephard , 1985 ,p 76).

As a result of the poor mechanical efficiency of the human body during most forms of exercise, physical activity places a specific load on the heat dissipating mechanisms of the body. These mechanisms for heat loss are evaporative heat loss through sweating (E), radiative heat loss (R), convective heat loss (C) and, to a much lesser extent, conductive heat loss (K) (Table 2.1).

The predominant mechanism employed for heat loss in a particular circumstance depends on environmental conditions (Nielsen , 1938) such as ambient temperature (Fig 2.1) , relative humidity of the atmosphere, and the presence or absence of wind. However, by far

TABLE 2.1

HEAT BALANCE IN MAN

HEAT GAINS	HEAT LOSSES
1) Metabolic	1) Convection
Basal metabolism	Ambient temperature
Specific dynamic action (food)	Air Currents
Physical exercise	2) Radiation (long wave)
Shivering	To surroundings and sky
Non-shivering thermogenesis	3) Peripheral vasodilatation
2) Radiation	4) Evaporation
Short-wave from sun	Insensible perspiration
Long-wave from surroundings	Thermoregulatory sweating
3) Ingestion : hot foods	Ventilation (panting)
4) Ventilation : hot climates	5) Conduction
5) Reduction of heat loss	Immersion in water
Periperal vasoconstriction	6) Reduction of heat gain
6) Behaviour	Behaviour
Clothing	Reduction of clothing
Artificial heating	Increased radiative body surface
	Cooler enviroment

Adapted from Bell et al (1980)

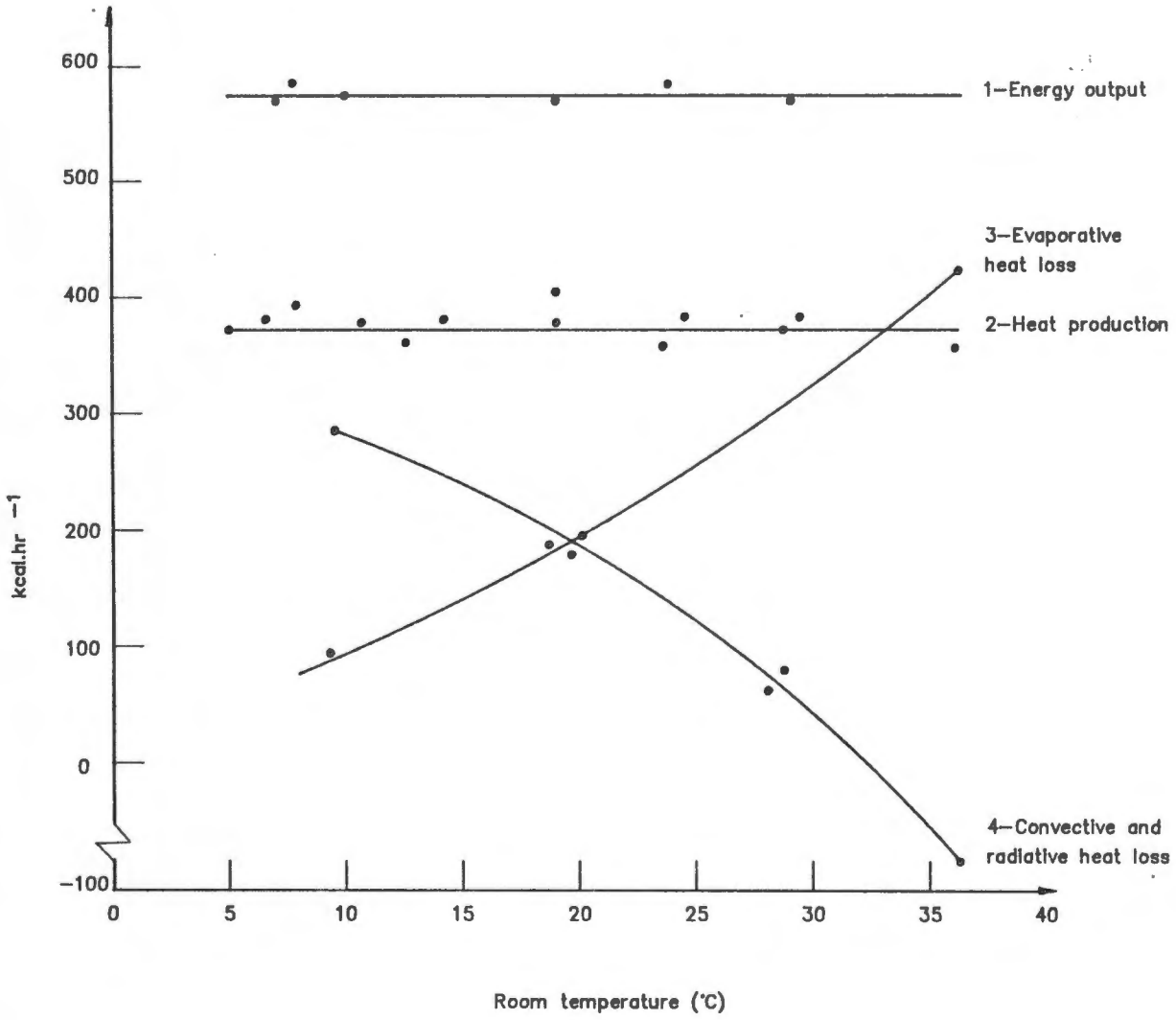

FIG 2.1. HEAT EXCHANGE DURING WORK (150 WATTS) AT DIFFERENT ROOM TEMPERATURES

AFTER NIELSEN (1938)

the most important mechanism for heat loss during physical activity is evaporative heat loss (Nielsen , 1938) (Fig 2.2).

These mechanisms of heat exchange and the factors that influence them will now be reviewed.

2.2.1 Evaporative heat loss: (E)

The amount of heat required to change unit mass of any substance, for example sweat, from the liquid to the vapor phase is called the latent heat of vaporization (Richards et al , 1962 ,p 310). The evaporation of sweat from the skin is the major mechanism of heat loss during physical activity (Nielsen , 1938). For every 1g (1ml) of sweat evaporation approximately 2,43 KJ of heat is lost (Shephard , 1985 ,p 400).

In addition to heat loss from sweat evaporation, the evaporation of water from the mucous membrane of the upper respiratory tract also contributes to heat loss during exercise (Shephard , 1985)

2.2.1.1 Factors affecting the evaporation of sweat during exercise:

A number of factors affect the rate of evaporation of sweat in the exercising human (Shephard , 1985 ,p 401). These include:

i) Skin temperature

Heat is supplied to the sweat film on the skin surface and this increases the energy of individual sweat molecules resulting in evaporation of sweat (Burns et al , 1975 ,p 152). A higher skin temperature therefore supplies more sweat molecules with sufficient energy for evaporation to occur. The rate of evaporative heat loss therefore depends in part on skin temperature.

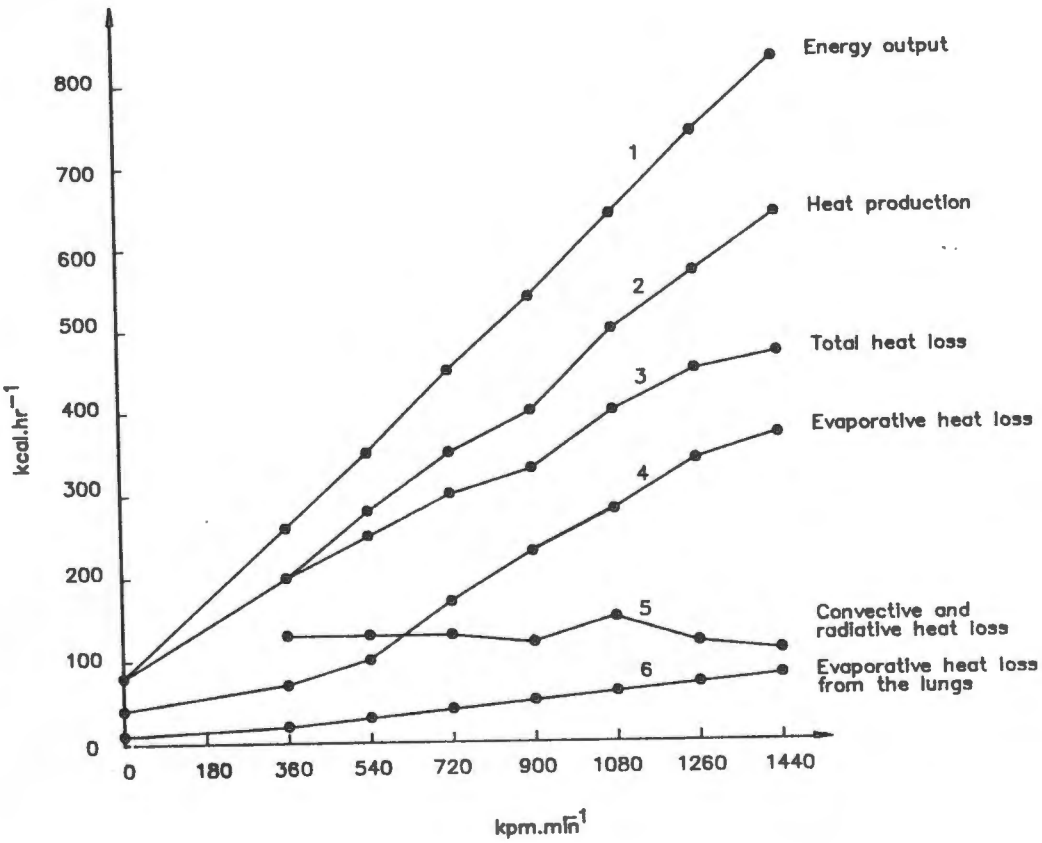

FIG 2.2 HEAT EXCHANGE AT REST AND DURING INCREASING WORK INTENSITIES AT ROOM TEMPERATURE

AFTER NIELSEN (1938)

ABBREVIATIONS : $kpm.min^{-1}$: kilopound metres per minute

$kcal.hr^{-1}$: kilocalories per hour

ii) The gradient of the water vapor pressure across the film of stationary air surrounding the skin

If a substance, for example sweat, occurs in both a liquid and a vapor phase, the vapor pressure is proportional to the temperature of the substance (Fig 2.3). At a specific temperature and pressure, the liquid and vapor will equilibrate and the vapor is then suturated. Further evaporation can only occur if the temperature of the substance increases or if the saturated vapor surrounding the liquid is removed, for example by air movement (Richards et al , 1962 , p 316).

iii) The thickness of the film of air on the skin surfaces exposed to air movement

It follows from (ii) that a rapid rate of removal of the air volume (area X thickness) surrounding the skin surface, will result in a constant state of disequilibrium between the liquid and vapor phases of sweat. Liquid will constantly change into vapor resulting in efficient evaporative heat loss.

iv) Clothing

Clothing can affect evaporative heat loss by the accumulation of sweat between the fabric and the skin. This results in trapping of air causing high humidity and therefore sweat evaporation will be poor.

An example of such clothing is the fabric nylon. Cotton in contrast, allows the passage of sweat through the fabric, thus exposing the sweat to ambient conditions such as air movement which then enhances evaporation (Bell et al , 1980 , p 418).

Detailed discussion of each of the factors that affect the mechanisms of heat exchange, as listed above, is beyond the scope

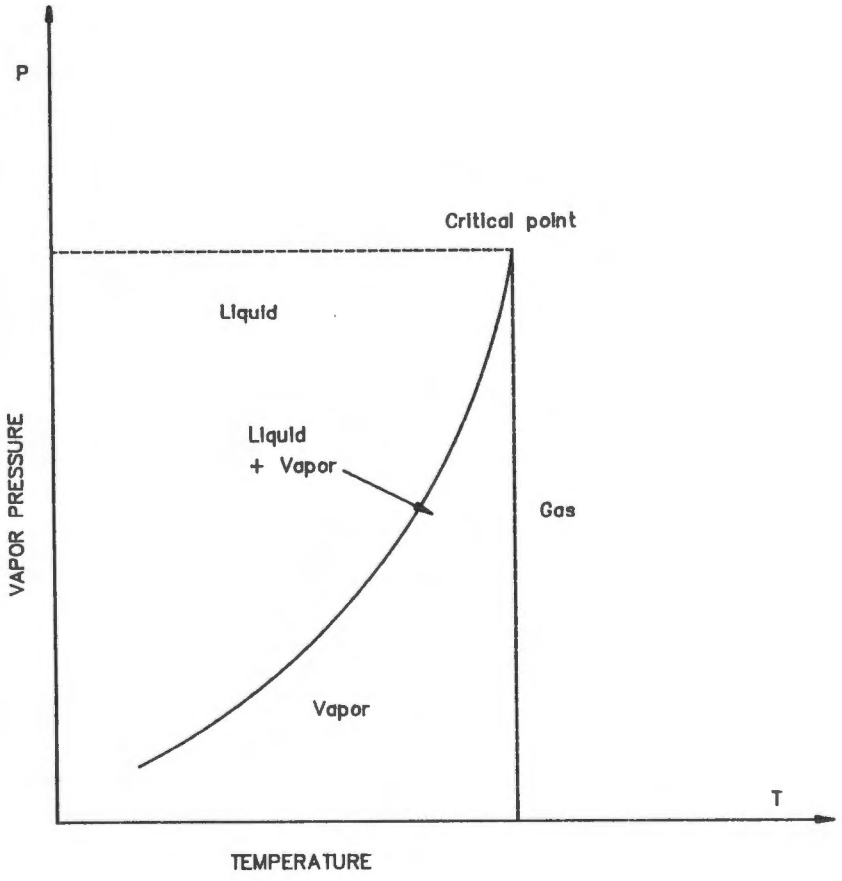

FIG 2.3 THE RELATIONSHIP BETWEEN VAPOR PRESSURE AND TEMPERATURE

AFTER RICHARDS ET AL (1975)

of this presentation. However, the role of skin temperature will be discussed in greater detail (Section 2.3.2)..

2.2.1.2 Factors affecting respiratory heat exchange:

Factors affecting respiratory heat exchange by evaporation include:

i) Minute ventilation

ii) The temperature difference between inspired and expired air

iii) The difference in humidity between inspired and expired air.

Respiratory heat exchange (RHE) can be calculated with the following equation (Deal et al , 1979).

$RHE = VE\ [HC(Ti-Te) + HV(WCi-WCe)]$ where :

RHE = Respiratory heat exchange ($kCal.min^{-1}$)
VE = Minute ventilation ($l.min^{-1}$)
HC = Heat capacity of air ($0,000304\ kCal.L^{-1}.{}^{o}C^{-1}$)
Ti = Inspired air temperature (^{o}C)
Te = Expired air temperature (^{o}C)
HV = Latent heat of evaporization ($0,58\ kCal.g^{-1}$)
WCi = Water content of inspired air ($mg.L^{-1}$)
WCe = Water content of expired air ($mg.L^{-1}$)

A more practical equation for extimating respiratory water loss has been reported by Mitchell et al (1972) based on experimental results obtained by McCutchan et al (1951).

Rate of water loss(me) = $0,019\ VO_2.(44-Pa)$ where

me = Rate of evaporative water loss ($g.min^{-1}$)
$\dot{V}O_2$ = Rate of oxygen consumption ($L.min^{-1}$ at STPD)
Pa = Ambient water vapor pressure

Mitchell et al (1972) established that this equation accurately predicts respiratory water loss during exercise at exercise intensities up to 80 % of the maximum aerobic capacity.

The evaporative water loss from the respiratory tract comprises only a small proportion of the total evaporative water loss during exercise under normal conditions (Bell et al , 1980 , p 413 : Fortney et al , 1985), and will therefore not be discussed further.

2.2.2 Conductive heat loss:(K)

Conduction is the transfer of thermal energy between two objects which are in direct contact with no interposing layer of air (Shephard , 1985 , p 400). Since there is little contact between the exercising human and other objects - except the ground and the soles of the feet - conductive heat loss is not significant during exercise in humans (Haymes et al , 1986 , p 7). However, conduction does play a role in the transfer of heat from the body core to the skin surface (Bell et al , 1980 , p559).

The rate of conductance of heat from the body core to the skin surface depends on (Burns et al , 1975 , p 153):

- The temperature difference between the body core and the skin.

- The thickness of the layer between the body core and the skin.

- The surface area of the conductive surface between the body core and the skin.

- The thermal conductance of the body which is defined as the inherent ability of the body tissues to transfer heat.

Mathematically this can be expressed by Fouriers law (Richards et al , 1962 , p 153):

H -K x A x (DO / DX) where

H = Rate of flow of heat
K = Thermal conductivity constant
A = Surface area
DO = Temperature gradient
DX = Thickness of the layer

The conductance of heat from the body core to the skin may differ in individuals for example in an obese person conduction is less efficient because (Haymes et al , 1986 , p 7):

- Subcutaneous fat increases the thickness of the layer between the body core and the skin and

- The thermal conductance of fat is poor.

It has also been shown that peripheral tissue conductance can be improved through heat acclimatization (Haymes et al , 1986 , p 38) by improving perfusion in the cutaneous interstitial space.

Conduction is therefore an important mechanism of heat transfer from the body core to the skin but does not play a significant role in heat exchange from the skin to the environment.

2.2.3 Convective heat loss:(C)

Convection is the transfer of heat induced by the movement of a gas or liquid (Burns et al , 1975 , p 155). Two types of convection occur:

2.2.3.1 Natural convection

The principle involved in natural convection is that a hot object transfers heat to the surrounding gas or liquid. The transferred heat alters the density of the gas or liquid, which by the force of gravity induces gas/liquid movement. This results in a constant flow of gas and liquid around the hot object.

Assuming that there will be a stagnant layer of gas and liquid near the surface of the hot object and that there is a non-linear drop in temperature across this layer, the rate of heat loss by natural convection can be expressed by the following equation (Burns et al , 1975 , p 156):

Rate of heat loss/unit area = $(O - Oo)^{1.25}$ where:
$O = T^{O}$ of the object
$Oo = T^{O}$ of the gas or liquid

2.2.3.2 Forced convection:

In forced convection the relative motion of the gas and liquid is maintained by an external force for example wind or a fan. If it is assumed that no stagnant layer of air is present, the rate of heat transfer is expressed by Newton's Law of Cooling (Burns et al , 1975 , p 156) ie:

Rate of heat exchange $\propto$ Area x Difference in temperature

The rate of heat exchange by convection can thus be expressed as follows (Burns et al , 1975 , p 156):

Rate of heat exchange & $A (O - Oo)^{n}$ where:

A = Area
O = Temperature of the object
Oo = Temperature of the environment
n = 1,25 for natural convection
n = 1 for forced convection

There are three main barriers to heat loss by convection in humans and these are (Shephard , 1985 , p 400):

i) Subcutaneous tissue

A thick layer of subcutaneous tissue will decrease conduction of heat from the body core to the skin. The skin temperature is therefore lowered and less heat will be lost by the heat exchange mechanisms convection, radiation and evaporation.

ii) Clothing

Inappropriate clothing, for example nylon, will trap sweat and air that surrounds the skin, thus hampering the rate at heat exchange (Bell et al , 1980 , p 418).

iii) The thin film of stationary air or water surrounding the skin

Heat loss at the surface of the skin can therefore be increased by (Shephard , 1985 , p 400):

i) Disturbing the stationary film of air or water

ii) Replacing the air with a gas of high thermal conductivity or

iii) Increasing the gas density, as occurs for example at sea level.

2.2.4 Radiation:(R)

Radiation is the transfer of heat in the form of electromagnetic waves (Haymes et al , 1986 , p 6). Two types of radiation are important in human heat exchange.

2.2.4.1 Short wave radiation

This form of radiation is solar radiation and originates at very high temperatures. Radiation of this type from humans to objects in space is negligable; therefore short wave radiation is always a method of heat gain for the individual performing outdoor activity.

2.2.4.2 Long wave radiation

Most materials emit and absorb radiation of this type. Whether heat is gained or lost by a particular object depends on the temperature differences between that object and surrounding objects and also the geometric relationships of the objects.

The total emissive power of an object is defined as the total radiant energy of all wavelengths emitted by the body per square meter of it's surface per second. The total emissive power of a body is mathematically expressed as (Burns et al , 1975 , p 157):

$E \propto T^4 e$ where:

E = Total emissive power
T = Absolute T° of the body
e = Emissivity constant

Clothing may offer a barrier between the exercising individual and the radiating element (Haymes et al , 1986 , p 6 ; Bell et al , 1980 , p 418). In this respect the colour of the clothing is important.It has been shown that when dark clothing is worn, solar radiation can cause a relative increase of the ambient

temperature up to three times its true value (Haymes et al , 1986 , p 6).

2.3 THE THERMOREGULATORY RESPONSE TO EXERCISE

The stress imposed on the human thermoregulatory system during exercise is primarily as a result of increased heat production. During maximal exercise the rate of heat production can increase up to 20 fold above that of the resting state (Shephard , 1985 , p 399 ; Haymes et al , 1986 , p 22). An extremely efficient heat dissipating mechanism must therefore exist to maintain the core body temperature within well defined limits of safety and optimal athletic performance.

Rises of core temperature above these limits can lead to a deterioration in the function of a variety of organs in the body and the clinical manifestations of heat associated illness have been well described (Kew et al , 1971 ; Clowes et al , 1974 ; Knochel , 1974 ; Wyndham , 1977 ; Anderson et al , 1983). Because exercise hyperthermia has also been implicated as a factor limiting work performance (Kozlowski et al , 1985 ; Segal et al , 1986), it becomes evident that effective heat dissipation is imperative for the elite athlete to achieve a maximal level of performance.

The surfaces at which heat exchange between the athlete and the environment can take place are limited to the skin and the mucous membranes of the respiratory tract. The mechanisms by which heat dissipation from these surfaces can occur in specific ambient conditions depend on :

- sweat production for evaporative heat loss and

- skin temperature for evaporative, convective and radiant heat loss.

The thermoregulatory response of the exercising individual is therefore designed to dissipate excess heat firstly by increasing the sweat production and secondly by increasing mean skin temperature.

These two mechanisms will now be discussed in some more detail.

2.3.1 Sweat production:

The accumulation of fluid on the skin surface occurs via two mechanisms (Fortney et al , 1985):

- Passive diffusion of water from epidermal cells.

- Active secretion of sweat from apocrine and eccrine sweat glands.

The passive diffusion of water to the skin surface contributes to insensible water loss and is estimated to be 4-13 $ml.hr^{-1}$ (Fortney et al , 1985). In general, the insensible loss during exercise is negligible (Fortney et al , 1985). Thus, the bulk of the discussion will concentrate on the active secretion of sweat.

2.3.1.1 Anatomy of the sweat gland

Two types of sweat glands apocrine and eccrine, are found in human skin (Fortney et al , 1985).

Apocrine sweat glands are derived from hair follicles and become functional only after puberty. It is believed that they fullfill a sexual function (Elizondo , 1977). Apocrine sweat glands secrete sweat containing large quantities of organic substances at slow rates (Fortney et al , 1985).

Eccrine sweat glands are derived from the epidermis and are the true thermal sweat glands. Between 2 and 5 million eccrine sweat glands are present in the average human skin; these are distributed over the skin surface in variable densities (Fortney et al , 1985). Each eccrine sweat gland consists of a simple tubular structure containing a secretory coil and a duct (Fig 2.4). The secretory coil is composed of 3 types of cells - clear (secretory) cells, dark (mucoid) cells and myoepithelial cells. Clear cells secrete precursor sweat but the functions of the dark cells and myoepithelial cells are still controversial (Sato , 1977). The duct consists of a double layer of cells and is coiled at first becoming progressively straighter. The active region, containing cells with high Na/K ATP-ase activity, is situated in the proximal portion of the duct.

The subsequent discussion will focus primarily on the function of the eccrine sweat gland.

2.3.1.2 Mechanism of sweat secretion:

Eccrine sweat glands are innervated mainly by sympathetic cholinergic fibres (Dale et al , 1934). Recent evidence indicates the existence of sympathetic adrenergic fibres to sweat glands and B adrenergic receptors have been demonstrated in the eccrine sweat gland (Sato , 1977). The specific role and function of the sympathetic adrenergic fibres to sweat glands is controversial (Kuno , 1965 ; Terada , 1966).

Sweat secretion occurs in two stages (Fortney , 1985):

Stage I:

Stage I involves the active secretion of Na^+ into the secretory coil of the gland with water following passively (Isotonic precursor sweat).

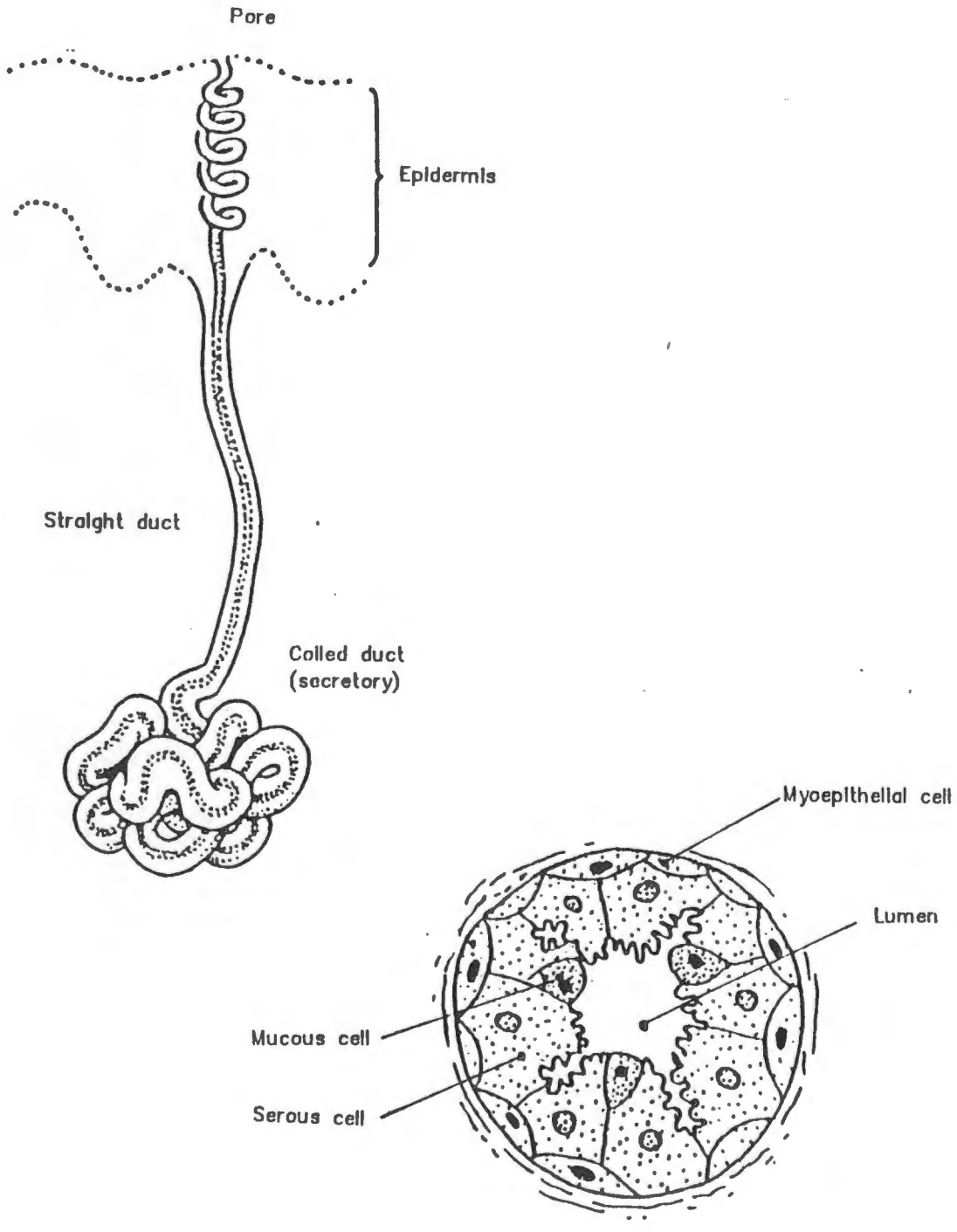

FIG 2.4 THE ANATOMY OF THE ECCRINE SWEAT GLAND

AFTER BELL ET AL (1980)

Stage II:

Stage II involves the active reabsorption of Na^+ ions from the sweat gland duct thus rendering sweat hypotonic (Hypotonic sweat production).

It follows that faster sweat rates reduce sweat transit time in the sweat duct. Therefore, less Na^+ is reabsorbed so that sweat becomes less hypotonic at higher sweat rates (Sato , 1977).

2.3.1.3 Factors affecting sweat output:

i) Neural:

Sweat production is under the direct control of the anterior hypothalamus (Haymes , 1986 , p 16). Afferent input to the anterior hypothalamus originates from thermoreceptors in the skin, upper gastro-intestinal tract, spinal cord and the hypothalamus itself (Fortney et al , 1985 ; Bell et al , 1980 , p 415). At a specific skin temperature, sweating is initiated (sweating threshold) and sweat rate then increases linearly with increasing skin temperature depending on the sensitivity of the sweat glands (sweating sensitivity) (Fig 2.5)

Factors affecting the relationship between skin temperature and sweat rate, for example endurance training and heat acclimatization, will be discussed later.

The role of sympathetic adrenergic innervation in the control of sweating is controversial (Fortney et al , 1985) but there is general agreement that adrenergic input during exercise increases the sweat rate.

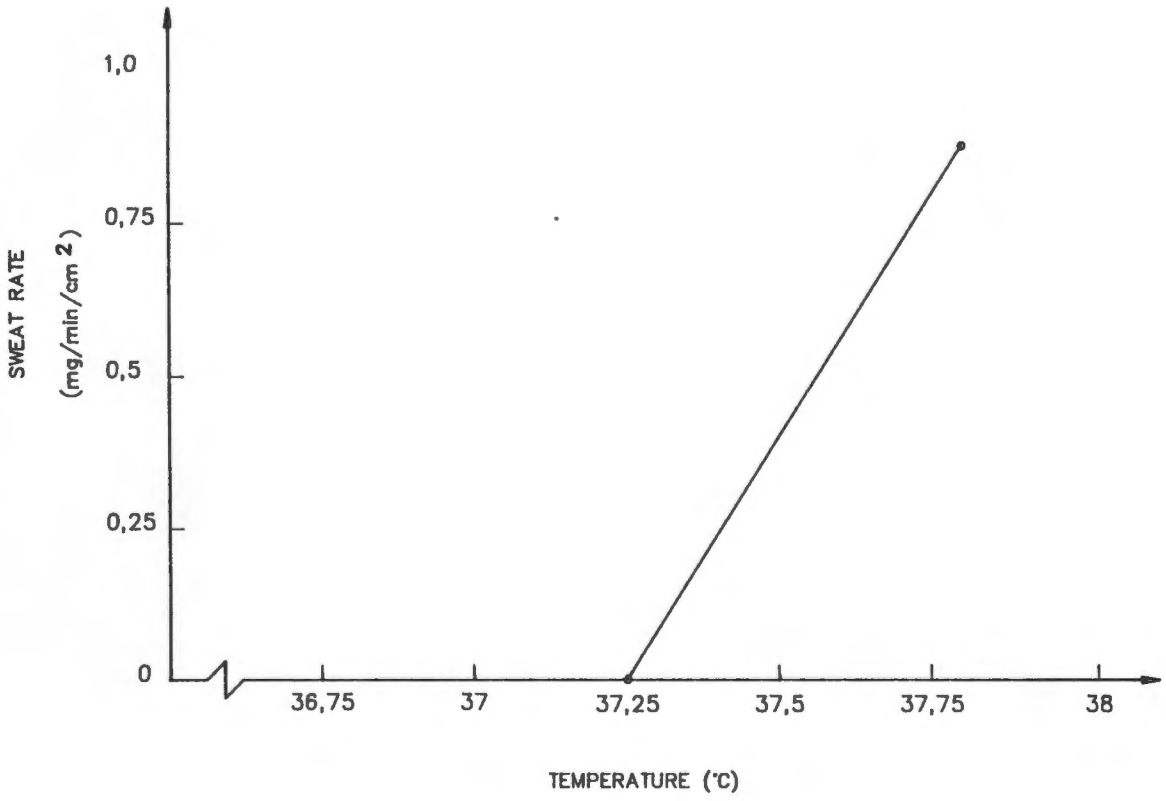

FIG 2.5 THE RELATIONSHIP BETWEEN CORE TEMPERATURE AND SWEAT RATE

AFTER TAYLOR (1986)

Calcium ions are required for both cholinergic and -adrenergic mediated sweating (Sato et al , 1981).

ii) Humoral agents:

A variety of humoral agents have been implicated as factors altering sweat rate.

a) Bradykinin:

Fox et al (1958) postulated that bradykinin may be an important mediator in sweat production. The mechanism may be that local production of bradykinin results in increased skin blood flow. (Brengelmann et al , 1981) (See section 2.3.2.2)

b) Aldosterone:

Aldosterone reduces sweat rate by increasing Na^+ absorption in the sweat duct. This alters the Na^+ and K^+ concentrations of the sweat (Sato , 1977).

c) Antidiuretic hormone: (ADH)

ADH does not appear to influence water and electrolyte secretion by the sweat gland in man (Sato , 1977). However it has been reported that ADH reduces sweat rate although the mechanism remains controversial and may be due either to vasoconstriction of cutaneous vessels (Sato , 1977) or to a direct effect on the hypothalamic control of sweating (Senay , 1979 ; Fortney et al , 1981).

d) Prostaglandin E :

The precise role of prostaglandin E in the sweat response is not well defined (Fortney et al , 1985) but it has been shown to have an inhibitory effects on sweat secretion (Elizondo , 1977).

iii) Osmolality:

Increases in plasma osmolality have been reported to decrease sweat rate (Nielsen , 1974a). The mechanism is postulated to be either a change in sweat gland function or a direct effect on the hypothalamus (Fortney et al , 1985).

Changes in plasma osmolality may either alter sweat gland sensitivity to a given neural input or result in alterations of the secretion-absorption process in the sweat gland itself (Fortney et al , 1985).

The decreased sweat rate associated with increased plasma osmolality may also be the result of a direct effect of serum osmolality on central osmoreceptors which then alter hypothalamic control of sweating.

iv) Specific ionic concentrations in blood and cerebrospinal fluid

Nielsen (1974b) has suggested that in addition to changes in plasma osmolality, the serum concentrations of specific ions can alter sweat production.

In particular it was suggested that the concentrations of serum Na^+ alone or the change in the Na^+/Ca^{++} ratio in serum can alter sweat output (Feldberg et al , 1970).

It was not possible to show whether the effects of Na^{+} and Ca^{++} were due to action on the central nervous system and thermoregulatory centers, or to peripheral interference with the function of sweat glands (Nielsen , 1974b).

v) Mechanical factors:

Hidromeiosis is defined as the decline in sweat rate during prolonged exercise in heat (Fortney et al , 1985). The precise mechanism for this decline in sweat rate is not known. It may be the result of mechanical blockage of the sweat gland duct by swelling of the epidermal cells (Frye et al , 1983). It is believed that increasing skin wetness causes swelling of epidermal cells resulting in duct blockage (Brown et al , 1965).

Collins et al (1965) however postulated that the mechanism of hidromeiosis is that prolonged elevations of body core temperture depress the effectiveness of sweating by altering central neural processes. This mechanism however needs to be investigated further (Fortney et al , 1985).

vi) Endurance training:

Endurance training was first reported to improve heat tolerance by Piwonka et al (1965). Since this report, controversy has existed in the literature regarding the role of endurance training in improving heat tolerance (Wyndham , 1973). Although training may reduce thermoregulatory strain during heat exposure of short duration, the beneficial effects of training are no longer adequate once exposure to hot humid conditions exceeds two hours (Strydom et al , 1966 ; Strydom et al , 1969). A combination of exercise and exposure to hot humid environments provides the best stimulus for improving heat tolerance.

The specific effects of endurance training on the sweat response are that sweat rate is increased following endurance training. The mechanisms responsible for this improved sweating are as follows (Henane et al , 1977 ; Fortney et al , 1985 ; Taylor , 1986).

a) A lowering of the core temperature threshold for sweating so that sweating occurs sooner after the onset of exercise (Fig 2.6) (Nadel et al , 1974 ; Henane et al , 1977 ; Taylor , 1986).

b) Increased sweat gland sensitivity; that is a steeper slope of the sweat rate to core temperature relationship (Fig 2.6) (Nadel et al , 1974 ; Henane et al , 1977 ; Sato et al , 1983 ; Taylor , 1986).

c) Increased sweat gland size (Sato et al , 1983).

d) Possible alterations in central neural processes may alter the central sweating mechanisms, as postulated by Fortney et al (1985).

e) Hofler (1968) and Shvartz et al (1979) reported that while total sweat volumes may be similar in trained and untrained subjects, the trained subjects exhibited increased sweat rates over the limb areas. This redistribution resulted in more efficient heat dissipation and a lowered core temperature at a given work load.

Improved skin blood flow also improves heat dissipation following endurance training and this will be discussed (Section 2.3.2.3).

vii) Heat acclimatization:

Heat acclimatization is the process by which repeated exposure to hot, humid environments improves the heat-dissipating function of

an individual. If this occurs artificially in a heat chamber, it is referred to as heat acclimation (Taylor , 1986).

The physiological effects observed following heat acclimatization are well described (Haymes et al , 1986 ,p 38) and are listed in Table 2.2. The specific effects of heat acclimatization on sweating and skin blood flow (Section 2.3.2.3), will be discussed.

One of the hallmarks of the heat acclimatized individual is that an increased sweat rate that is observed.

Several mechanisms appear to be responsible for this improved sweating response.

a) A lowering of the central drive point for sweating follows heat acclimatization, and will result in the initiation of sweating at a lower body core temperature (Nadel et al , 1974) (Fig 2.6).

b) It is postulated that increased sensitivity of the sweat glands to a given stimulus contribute to the higher sweat outputs measured following heat acclimatization (Sato et al , 1983) (Fig 2.6).

c) The metabolic function of the sweat gland may alter following heat acclimatization. It has been demonstrated that glycogen depletion in the secretory cells of sweat glands normally observed following vigorous sweating, does not occur in the heat acclimatized individual (Dobson , 1960).

2.3.2 Skin temperature

An increase in skin temperature can result in significant heat loss through convection, radiation and conduction (Section 2.2) provided the ambient temperature is lower than skin temperature.

TABLE 2.2

PHYSIOLOGICAL CHANGES OBSERVED DURING EXERCISE AFTER HEAT ACCLIMATIZATION

Heart rate - decrease
Stroke volume - increase
Core temperature - decrease
Skin temperature - decrease
Sweat output - increase
Evaporated sweat - increase
Onset of sweating - earlier
Wetted body surface - increase
Skin and core temperature at onset of exercise - decrease
Sodium chloride in sweat - decrease
Work output - increase
Subjective discomfort - decrease
Fatigue - decrease
Coordination - increase
Work capacity - increase
Mental disturbance - decrease
Syncopal response - decrease
Extracellular fluid volume - increase
Plasma volume - increase
Nausea - decrease
Vomiting - decrease

Adapted form Haymes et al (1986)

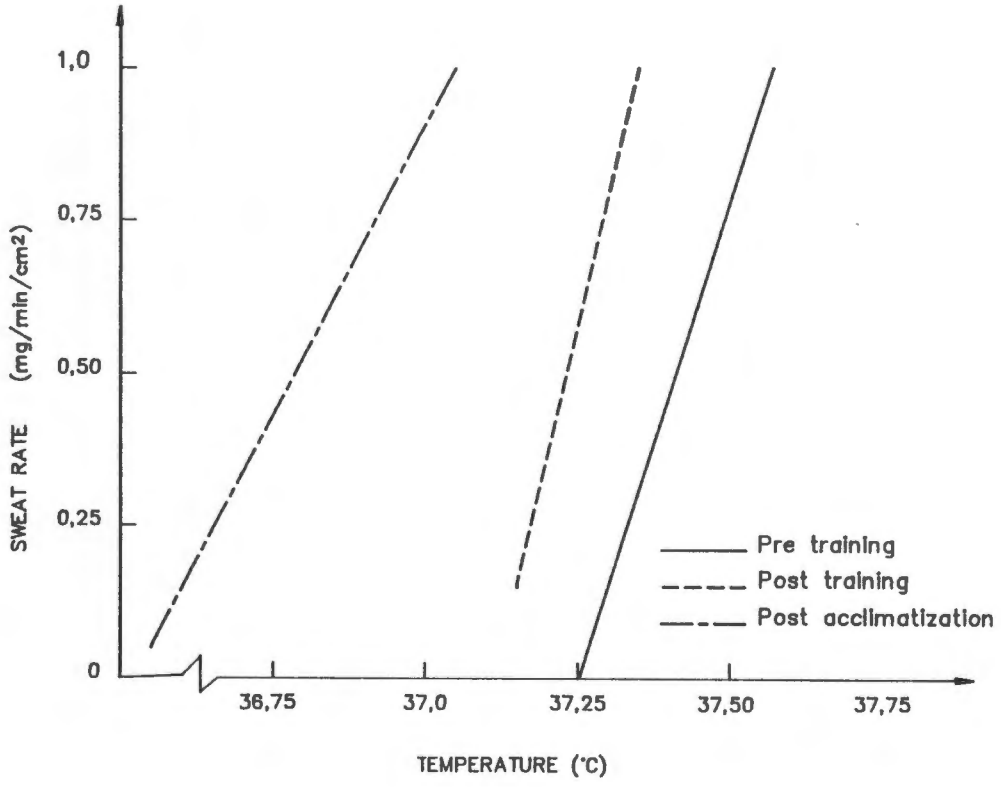

FIG 2.6 THE EFFECTS OF PHYSICAL TRAINING AND HEAT ACCLIMATIZATION ON THE CORE TEMPERATURE TO SWEAT RATE RELATIONSHIP

AFTER FORTNEY ET AL (1985)

When ambient temperature is higher than mean skin temperature the gradient for heat exchange is reversed, and heat transfer occurs from the air to the skin resulting in heat storage rather than heat loss. In general this occurs at ambient temperatures higher than 32^{o}C to 34^{o}C (Fortney et al , 1985).

Skin temperature increases in response to exercise induced rises in core temperature by two mechanisms:

- Heat transfer by conduction (Section 2.2.2) from the body core.

- Increased skin blood flow.

The transfer of heat from the body core to the skin by conduction and the factors affecting it have already been discussed (Section 2.2.2).

2.3.2.1 Skin blood flow:

Blood flow to the skin has two main functions that is to provide nutrition to the skin tissues and to regulate skin temperature for heat transfer to the environment. In order, to perform these two functions three different types of blood vessels are found in the skin (Fig 2.7).

i) Nutritive arteries, capillaries and veins to provide nutriton to the skin.

ii) Subcutaneous venous plexuses are present to hold large volumes of blood under the skin surface so that heat exchange can occur.

iii) Arteriovenous anastomoses are present on the volar aspects of the hand, the feet, lips, nose and ears. The muscular walls of the arteriovenous anastomoses are innervated by sympathetic

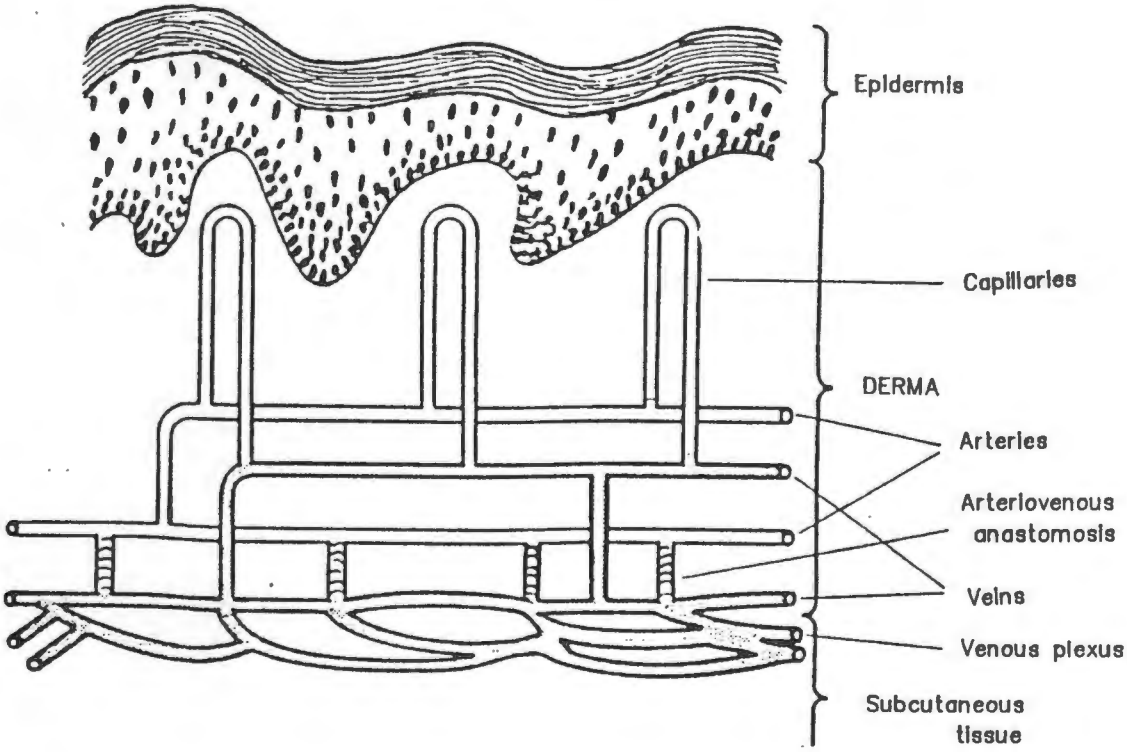

FIG 2.7 THE ANATOMY OF THE SKIN BLOOD VESSELS

AFTER GUYTON (1986)

vasoconstrictor fibres which then regulate blood flow to the venous plexuses.

2.3.2.2 Skin blood flow at rest:

Skin blood flow rates at rest are variable and could be as little as 50 ml per minute in cold conditions, increasing to 3000 ml per minute in extreme heat. During exercise the rate could be even higher. Normal skin blood flow under neutral ambient conditions is about 250 ml/sq meter of body surface area (400 ml per minute in the average adult). The factors affecting the control of blood flow in resistance vessels of the skin are indicated in Table 2.3.

Since most of the blood flowing through the skin functions to control body temperature, the principle regulator of skin blood flow is nervous output from the temperature control centre situated in the anterior hypothalamus. This control is facilitated primarily through a network of sympathetic vasoconstrictor fibres secreting norepinephrine at their nerve endings. Changes in hypothalamic temperature (Astrand et al , 1977) as well as afferent signals from temperature receptors situated in the skin and probably in other deeper areas of the body (Haymes et al , 1986) affect hypothalamic neural output. This then alters the vasoconstrictor tone of the skin blood vessels. Free circulating catecholamines also affect skin blood vessels directly (Table 2.3).

Vasodilation of the skin blood vessels occurs when the sympathetic vasoconstrictor mechanism is inhibited following an increase in core temperature. In addition it has been postulated that active vasodilation can occur either by direct sympathetic cholinergic vasodilatory mechanisms or by secondary vasodilation occurring as follows: (Guyton , 1986 , p 345) Increased sweating may release the enzyme kallikrein which splits bradykinin from globulin found in the interstitial fluid. Bradykinin in turn is

TABLE 2.3

FACTORS AFFECTING THE CONTROL ON BLOOD FLOW IN RESISTANCE VESSELS OF THE SKIN :

1. Local control :

   a. Metabolic factors associated with the dilatation of resistance vessels

      Carbon dioxide, Excess hydrogen ions, Hypoxia, Hyperkalaemia, Increased osmolality, Adenosine triphosphate, Adenosine, Phosphate, Bradykinin

   b. Temperature

      Increased local temperature causes vasodilatation
      Decreased local temperature causes vasoconstriction

   c. Transmural pressure

2. Nervous control :

   a. Vasoconstrictor nerves controlled by the vasomotor centre
   b. Vasodilator cholinergic nerves in the parasympathetic and sympathetic systems

3. Vasomotor reflexes :

   a. Thermoregulatory reflexes
   b. Blood shift reflexes
   c. Chemoreceptor reflexes
   d. Emotional stress reflexes
   e. Lung inflation reflexes

4. Hormonal control :

   a. Adrenalin and noradrenalin - vasoconstriction
   b. Angiotensin - vasoconstriction
   c. Bradykinin - vasodilatation
   d. Histamine - vasodilatation

Adapted from Bell et al (1980)

a powerful vasodilator acting directly on skin blood vessels. Other peptides have also been suggested to cause vasodilation (Guyton , 1986 , p 345).

2.3.2.3 Skin blood flow during exercise:

During physical exercise blood flow to the working muscle increases as a result of both an increase in cardiac output as well as redistribution of blood flow away from the viscera to the muscle (Table 2.4). At the onset of exercise transient vasoconstriction of the skin vascular bed occurs probably as a result of sympathetic vasoconstrictor responses associated with the onset of exercise (Fortney et al , 1985).

As the physical activity progresses and core temperature increases, central and peripheral thermoreceptors are activated. The resultant stimulation of the anterior hypothalamus initiates vasodilation of skin blood vessels by mechanisms described in Section 2.3.2.2. The core temperature at which this vasodilatation is initiated is known as the vasodilatory threshold. As core temperature increases further, skin blood flow will increase linearly (Fig 2.8).

Severe prolonged exercise will eventually result in a loss of the skin blood flow to core temperature relationship. At this point (vasomotor vasoconstrictor response), if core temperature increases further, skin blood flow will not increase and eventually decrease at very high core temperatures (Fig 2.9).

The mechanisms accounting for this phenomenon are:

- The blood volume decreases as a result of sweating and fluid shifts from vascular to interstitial compartments. The resultant dehydration activates baroreceptors which in turn activate the vasomotor centre which then causes vasoconstriction in the skin blood vessels.

TABLE 2.4

REDISTRIBUTION OF BLOOD FLOW DURING EXERCISE

	REST (ml)	STRENUOUS EXERCISE (ml)
Splanchnic	1 400	600
Renal	1 100	600
Cerebral	750	750
Coronary	250	750
Skeletal muscle	1 200	12 500
Skin	500	1 900
Other organs	600	400
Cardiac output	5 800	17 500

Adapted from Clarke (1975)

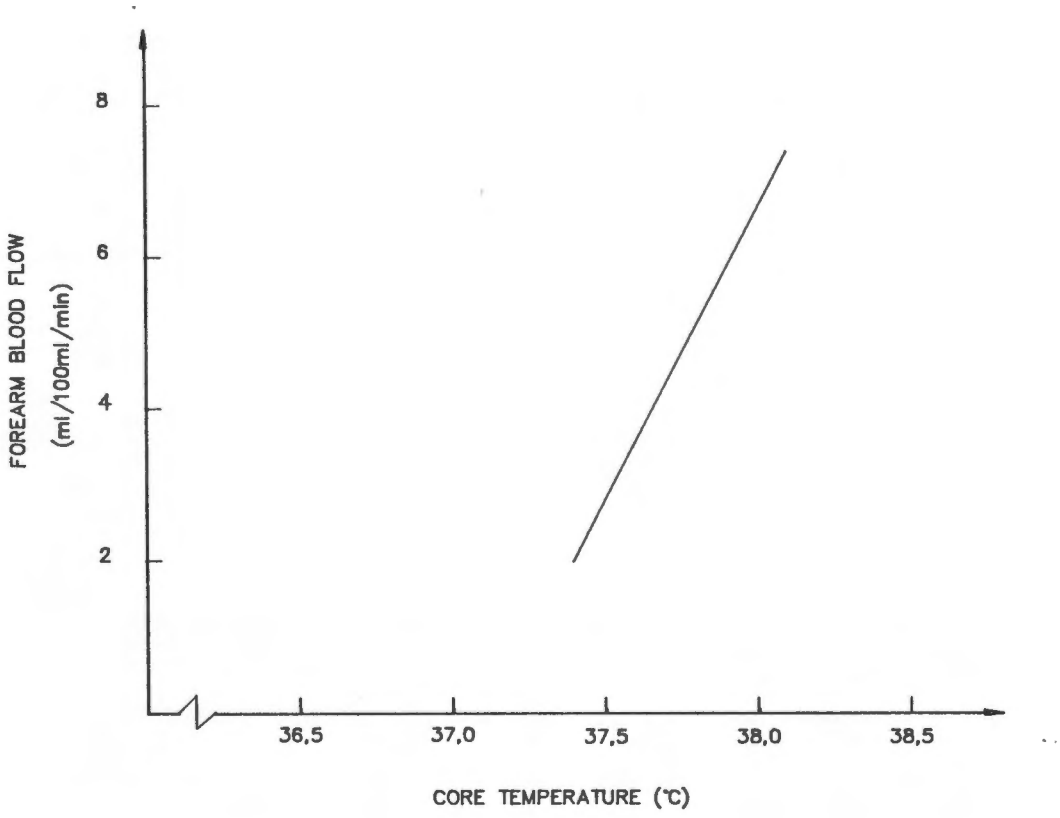

FIG. 2.8. THE RELATIONSHIP BETWEEN CORE TEMPERATURE AND FOREARM BLOOD FLOW

AFTER FORTNEY ET AL (1985)

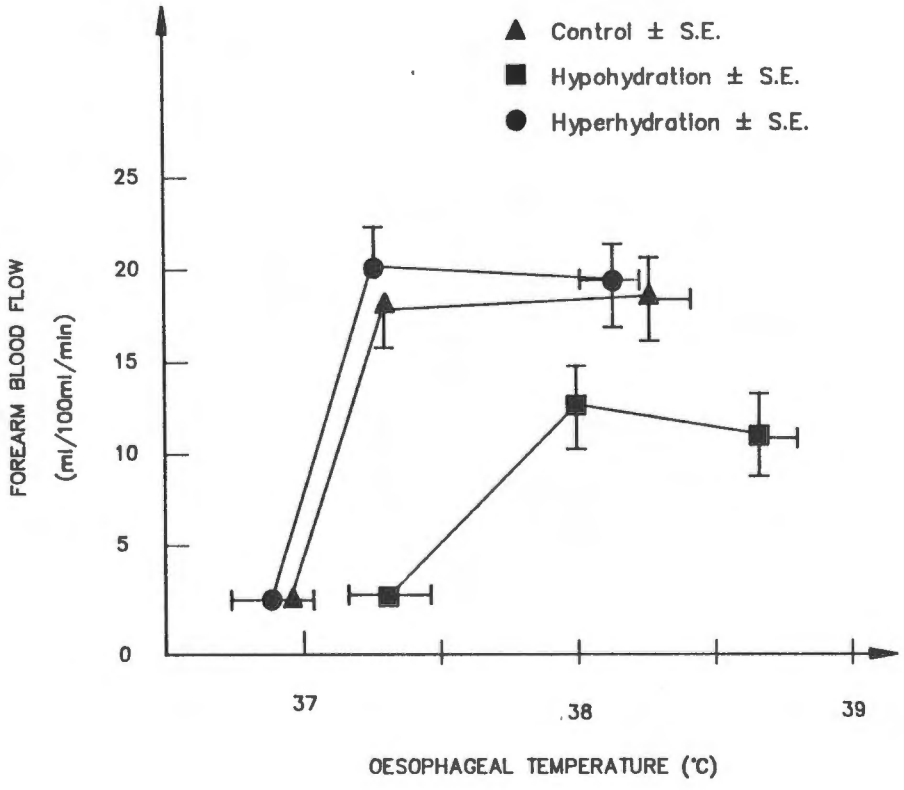

FIG 2.9 THE EFFECT OF HYDRATION STATE ON THE FOREARM BLOOD FLOW – CORE TEMPERATURE RELATIONSHIP

AFTER NADEL ET AL (1980)

- Blood flow is redistributed away from the skin to the working muscle for provision of oxygen and fuel and for the removal of products of metabolism.

A number of factors can alter the vasodilatory threshold, skin blood flow to core temperature relationship and the onset of the vasomotor vasoconstrictor response.

i) Hydration:

Nadel et al (1980) demonstrated that diuretic induced hypovolaemia prior to exercise elevated the vasodilatory threshold . This resulted in greater heat storage and elevated exercise core temperatures in the hypovolaemic group. However hyperhydration did not significantly alter the core temperature skin blood flow relationship.

Adequate hydration during exercise will ensure the maintenance of an adequate blood volume for much longer and thereby delay the dehydration induced vasomotor vasconstrictor response described above. Adequate heat loss through an increase in skin blood flow can occur provided the subject is well hydrated both at the onset and during exercise.

A recent report demonstrated that pre-exercise hyperhydration results in lower core temperatures during exercise. The mechanisms are related to earlier sweating as well as lower sweat volumes (Grucza et al , 1987)

.

ii) Posture:

Johnston et al (1974) demonstrated that exercise performed in the upright position decreases the slope of the skin blood flow to core temperature relationship (Fig 2.10). In the upright position there is considerable pooling of blood in the lower extremities. As a result venous return is lower than during

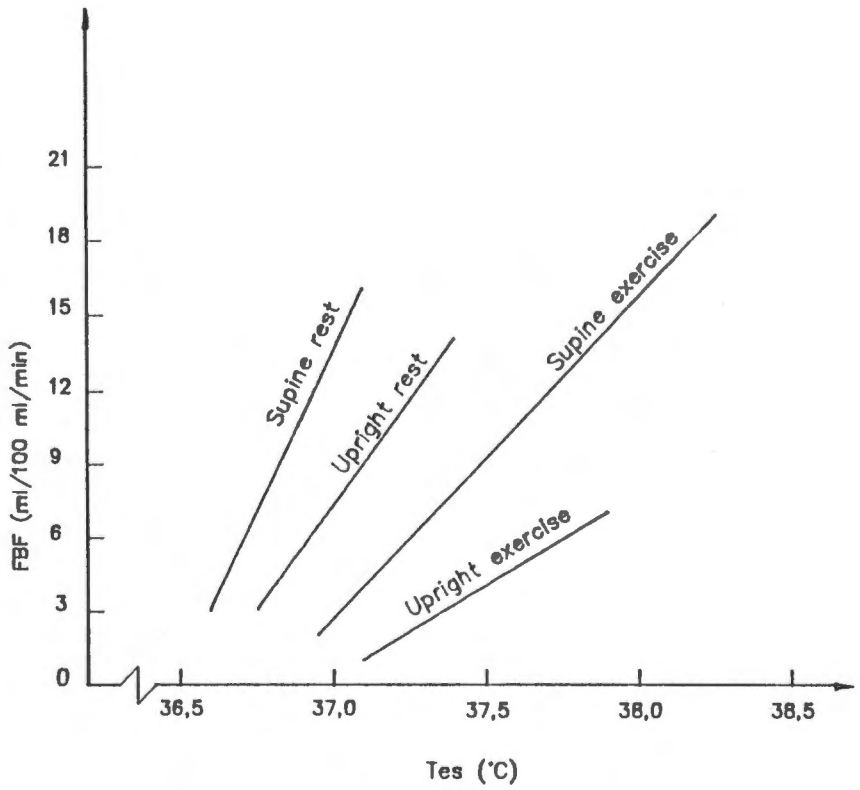

FIG 2.10 THE EFFECT OF POSTURE ON THE FOREARM BLOOD FLOW (FBF) – OESOPHAGEAL TEMPERATURE (Tes) RELATIONSHIP

AFTER FORTNEY ET AL (1985)

supine exercise (under similar conditions) and therefore cardiac output is lower. For exercise in similar conditions less blood is therefore distributed to the skin vasculature. In addition Bevegard et al (1977) showed that arterial baroreceptors are more sensitive during upright exercise in the heat. It follows that the vasomotor vasoconstrictor mechanism will operate when small decreases in venous return are detected resulting in vasoconstriction of skin blood vessels.

These results have been confirmed by Roberts et al (1980) and this group further demonstrated that this decrease is accentuated by higher skin temperatures.

iii) Heat acclimatization

The physiological adaptations observed after heat acclimatization as well as the techniques employed to acclimatize individuals are well described (Table 2.2).

The effects of heat acclimatization on skin blood flow have been described by Roberts et al (1977). It appears that heat acclimatization lowers the vasodilatory threshold without altering the skin blood flow to core temperature relationship (Fig 2.11). This results in higher skin blood flow rates after acclimatization for similar core temperatures which in turn improves heat dissipation.

iv) Endurance training

The improved sweating in response to training has already been discussed (Section 2.3.1.3). In addition it appears that following physical training, skin blood flow at a given core temperature is higher through a reduction in the vasodilatory threshold (Fig 2.11). The slope of the skin blood flow to core temperature relationship remains unaltered (Fortney et al , 1985).

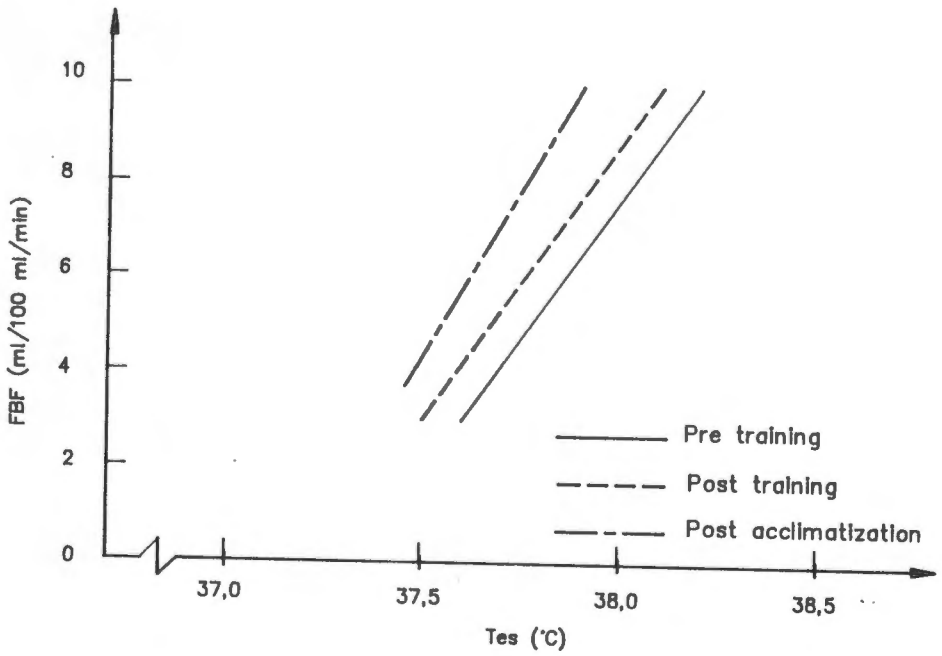

FIG 2.11 THE EFFECT OF TRAINING AND HEAT ACCLIMATIZATION ON THE FOREARM BLOOD FLOW (FBF)– OESOPHAGEAL TEMPERATURE (Tes) RELATIONSHIP

AFTER FORTNEY ET AL (1985)

2.4 Summary

The body temperature of man both at rest and during physical activity must be maintained within a narrow range. Heat gained by the body must therefore be balanced by heat loss. The mechanisms that exist for maintaining thermal equilibrium in man are metabolic heat production, evaporative heat transfer, radiant heat exchange, convective heat transfer and conductive heat transfer. Physical exercise, in which external work is performed, imposes a strain on the heat dissipating mechanisms of the body particularly if hot, humid environmental conditions exist. The most important mechanism for heat exchange during exercise is evaporative heat loss by sweating. A second mechanism, increasing skin temperature, will apart from enhancing sweat evaporation, also facilitate heat loss through radiation, convection and to a much lesser degree conduction.

During exercise eccrine sweat glands, under control of the anterior hypothalamus through sympathetic cholinergic fibres, are activated at a given skin temperature (sweating threshold). Sweat rate will then increase linearly with the increase in temperature depending on the sweat gland sensitivity. A number of factors such as neural control mechanisms, humoral agents, serum ionic concentrations, serum osmolality, mechanical blockage of sweat ducts, endurance training and heat acclimatization influence this sweat rate to skin temperature relationship during exercise.

An increase in skin blood flow is the most important mechanism to increase the skin temperature. Specific blood vessels regulating skin blood flow are under control of the sympathetic nervous system. At the onset of exercise vasoconstriction occurs with resultant decreased skin blood flow. As core temperature increases beyond a specific threshold the vasodilatory reflex is

initiated by the thermoregulatory centre situated in the anterior hypothalamus. A further increase in core temperature will result in an increase in skin blood flow. After prolonged exercise, skin blood flow cannot be maintained because of sweat induced dehydration and excessive demands made on the cardiac output by increases in muscle blood flow. The resultant decreased skin blood flow increases the rate of body heat storage. The factors that can influence skin blood flow during exercise are the state of hydration of the subject, the posture, endurance training and heat acclimatization.

In this chapter the principles of thermoregulatory physiology during exercise, have been outlined. A study of the affect of any substance on thermoregulation during exercise is based on these principles. Such a substance, for example an endogenous opioid, may influence thermoregulatory function by acting at a number of different levels such as the anterior hypothalamic control of thermoregulation, autonomic nervous system, sweat gland fucntion, skin blood flow, cardiovascular and fluid dynamics, respiratory function, or metabolic heat production.Endogenous opioids may even affect the production, metabolism or secretion of humoral agents, hormones or other substances involved in thermoregulatory physiology.

The existing literature regarding the role of endogenous opioids in thermoregulation during exercise will now be reviewed.

CHAPTER THREE

LITERATURE REVIEW: ENDOGENOUS OPIOIDS AND THERMOREGULATION

3.1 INTRODUCTION

In order to review the existing literature on the possible role of the endogenous opioid system in thermoregulation during exercise, it is important to discuss the following aspects of the endogenous opioids:

- History of the discovery of the endogenous opioid system.
- Terminology and classification.
- Methods of investigating the endogenous opioid system.
- Endogenous opioids in exercise.
- Endogenous opioids and thermoregulation.

3.2 HISTORY OF THE DISCOVERY OF THE ENDOGENOUS OPIOID SYSTEM

Opium, obtained from the unripe seed capsule of the poppy, Papaver somniferum, has been known to man from ancient times. The Sumerians used an ideograph to describe the poppy as a "joy plant" as long ago as the fourth millenium BC. Opium, derived from the Greek word for "juice", was used by the Arabian physician Avicenna (980-1037). The analgesic properties, as well as the pleasurable sensations induced by the substance, made it an ideal form of medication and was recommended in the treatment of disease by John Wesley in 1747. Morphine an alkaloid derivative of opium is still used commonly today (Girdwood , 1976 , p 142).

The demonstration by Paton (1957) and Schaumann (1957) that morphine has specific neurotransmitter properties started investigators on the path of discovery of the endogenous opioid system. This discovery is stated to be a classic story of intelligent science and unfolding orderliness (Copolov et al , 1983). The first specific opioid receptor was discovered by Goldstein et al (1971) and this finding was confirmed two years later by two other independant investigators (Pert et al , 1973 ;Simon et al , 1973). However, it was only two years later that Hughes et al (1975) characterized the first two opioid pentapeptides, methionine- and leucine-enkephalin followed later by the discovery of B-endorphin (Li , 1977). Since then many different endogenous opioids and opioid receptors with different properties have been discovered (Section 3.3). It is still a popular field of investigation today.

Despite extensive and continuous investigation following the discovery of these substances, their precise physiological role has not yet been established (Kosterlitz , 1980). Conflicting findings regarding the pathophysiological role of these

substances are the result of difficulties experienced when attempting to investigate this system. These difficulties have been described by Copolov et al (1983) and briefly mentioned are:

3.2.1 Assay systems :

Although many different assay systems are available to detect and quantitate opioid peptides (Kuhar et al , 1984 , p 10) these systems often lack specificity and sensitivity (Copolov et al , 1983). An example, is that the collection of specimens has to be faultless because of rapid degradation of the peptide . In general, care must be taken when interpreting and comparing the results of different studies as different antisera may also have different degrees of cross reactivity (Kuhar et al , 1984 , p 11).

3.2.2 Antagonists :

The most commonly used antagonist, naloxone hydrochloride, is relatively selective for one receptor type only and the consequences of occupancy of other receptor types (Table 3.1) cannot be studied using this technique (Chang et al , 1981).

3.2.3 Tissue concentration :

The concentrations of opioids differ in tissues and even in tissue regions, such as occurs in the brain. This makes the interpretation of findings and their extrapolation to physiological events difficult (Copolov et al , 1983). In exercise studies plasma levels of opioids are commonly measured, (Harber et al , 1984) but because the blood brain permeability differs for different opioids these findings cannot be interpreted as necessarily reflecting intra-cerebral events.

TABLE 3.1

CLASSIFICATION OF OPIOID RECEPTORS

Receptor	Bioassay	Naloxone antagonism	Endogenous ligand	Principal location
Mu	Guinea pig ileum	Sensitive	? Endorphin	Hypothalamus Peri-aquaductal gray matter
Delta	Mouse vas deferens	Resistant	Met/Leu-enkephalin	Limbic system Basal ganglia
Kappa	Rabbit vas deferens	Resistant	Dynorphin	Substantia nigra Posterior pituitary
Epsilon	Rat vas deferens	Sensitive	Endorphin	?
(Sigma)	-	Highly resistant	?	?

Adapted from Grossman et al (1985)

These difficulties serve to encourage investigators to pursue further study into the endogenous opioid system and to define it's role in a variety of pathophysiological processes.

3.3 TERMINOLOGY AND CLASSIFICATION:

The term "endorphin", coined from **endogenous morphine** , is often used incorrectly to refer to all classes of endogenous opioids. In this discussion "endorphin" will only refer to the specific 31 amino acid residue derived from pro-opiomelanocortin (Table 3.2).

The endogenous opioid peptides are usually classified according to their precusor substances, and the classification used in this discussion is the one described by Copolov (1985) (Table 3.2). Other investigators have used different classifications (Kuhar et al , 1984 ; Imura et al , 1981). It is important to note that although most endogenous opioids are peptides, there are reports of non-peptide endogenous opioids (Gintzler et al , 1976 ; Killian et al , 1981). These, however, are not included in the classification described Table 3.2.

In addition to the different classes of endogenous opioids that have been described, Martin et al (1976) proposed the existence of separate classes of opioid receptors. The subsequent discovery of at least five different opioid receptor classes has been made possible by studying bioassay tissues from various sources utilizing a variety of opioid agonists and antagonists.

On the basis of results from such studies Grossman et al (1985) proposed a classification for opioid receptors (Table 3.1). It is important to mention that Lee et al (1980) suggested that there might be a single opioid receptor which can convert to one of several ligand - specific states. This has been supported by a study showing that mu and delta forms of the opioid receptor in rat striatum can interconvert (Bowen et al , 1981).

TABLE 3.2

CLASSIFICATION OF ENDOGENOUS OPIOIDS

Precursor	**Sites**	**Derivatives**
Pro-opiomelanocortin	Pituitary gland	ACTH*
		B-lipotropin
	Brain (Medial basal hypothalamus)	A MSH*
		B-endorphin
Pro-enkephalin	Adrenal medulla	Met-enkephalin
	CNS*	Arg^6 phe^7
	GIT*	Leu-enkephalin
Pro-dynorphin	Hypothalamus	Dynorphin A
	Brainstem	Dynorphin B
	Amygdala	A-Neoendorphin
	GIT*	Leu-enkephalin

*:CNS=Central nervous system; GIT=Gastro-intestinal tract

Adapted from Copolov et al (1985)

3.4 METHODS OF INVESTIGATING THE ENDOGENOUS OPIOID SYSTEM:

The investigation of the endogenous opioid system has never been an easy task and some of the problems that are encountered have already been mentioned (Section 3.2). The direct measurement of opioid peptides in tissue or body fluid by various assay techniques is commonly performed. However, each of these assay systems is associated with problems and pitfalls (Kuhar et al , 1984 ; Grossman et al , 1985).

The bioassay which is an essential investigation to describe the biological activity of opioids, is very non-specific. Similarly the radioreceptor assay, which is simpler to use and very rapid, is also non-specific. The radio-immunoassay, with its related immunohistochemical techniques, has become the most important technique for the measurement of opioid peptides (Grossman et al , 1985). However, the radio-immunoassay depends on firstly the specificity and sensitivity of antisera used and secondly the purity of standards and the substances used when tests for cross reactivity are performed (Grossman et al , 1985).

The other very common method of assessing the endogenous opioid system is to observe physiological responses when the specific opioid antagonist naloxone hydrochloride is administered. This indeed was the method used in this study, and it is therefore appropriate to review the advantages and limitations of this method of investigation.

Although naloxone is described by Jaffe and Martin (1980) as a "relatively pure antagonist" it appears that it may also have other pharmacological properties. These properties have been thoroughly reviewed by Sawynok et al (1979) and will be discussed briefly.

Firstly, it has been demonstrated that high doses of naloxone can have agonist properties similar to morphine. Naloxone also appears to influence the pharmacological responses to a variety of non-opioid drugs such as :

- Anti-nociceptive agents eg. nitrous oxide, haloperidol.

- General anaesthetic agents eg. cyclopropane, halothane.

- Dopaminergic active drugs eg. chlorpromazine, d-amphetamine.

- Drugs interacting with the GABA(Gamma-aminobutyric acid)-ergic system eg. diazepam.

- Other miscellaneous agents eg. lysergic acid diethylamide (LSD), acetylcholine and nicotine.

As already mentioned, it appears that when different doses of naloxone are used, contrasting physiological responses may be elicited. This has indeed been demonstrated in a number of studies including studies performed to document the effects of naloxone administration on the hormonal response to exercise (Haier et al , 1981). These dose-dependent effects may be explained by the fact that there are naloxone sensitive receptors (mu receptor, epsilon receptor) and naloxone insensitive receptors (delta receptor, kappa receptor) which would then exert their effect at low doses and high doses of naloxone respectively (Table 3.1). The low dose used in most studies on human subjects ranged from 1 to 5 mg naloxone and the high dose ranged from 7 to 10 mg (Sawynok et al , 1979). These dosages apply to the adult human of average body weight (70 kg).

Naloxone hydrochloride is available only in injectable form because of its rapid hepatic first pass metabolism after oral administration (Nutt et al , 1974). Following its administration, naloxone enters the brain rapidly (initial brain

to serum concentration of 5:1) but also leaves the brain rapidly to enter the plasma. Its reported mean serum half life is 64 minutes in humans with a range of 30 to 81 minutes (Ngai et al , 1976). The relatively short duration of action and the need for parenteral administration may be considered two futher limitations in its use.

Having highlighted the limitations of using naloxone-mediated receptor antagonism to investigate the endogenous opioid system, the following arguments make this method of investigation the preferred one in our study.

Firstly, naloxone is still widely used to investigate the endogenous opioid system and its greatest critics, Sawynok et al (1979), state that "antagonism by naloxone is a necessary but not sufficient criterion for invoking the mediation of a response by an endogenous opiate". An investigation using naloxone is not only necessary but imperative in this study in order to compare these results to those of previous studies where naloxone was also used to investigate this system (De Meirleir et al , 1985).

Secondly, because this technique is easy to use, and relatively inexpensive, it serves as a useful screening method for implicating the endogenous opioid system in any physiologic process.

Thirdly, because naloxone acts on receptors situated both within the central nervous system and the periphery, it is the ideal method to evaluate thermoregulatory responses which have both central and peripheral components.

Fourthly, because endogenous opioids may act directly on the hypothalamic thermoregulatory control centre, (Imura et al , 1981), they may bind to the naloxone sensitive mu receptors which are found in high concentration in the hypothalamus (Table 3.1).

The use of naloxone as an investigative tool in studies on thermoregulation is therefore appropriate.

Finally in an attempt to reduce the risk of inaccurate findings, both a low dose (2 mg) and a high dose (10 mg) of naloxone were used in Part I of the study.

It is quite clear that no single method of investigation is ideal and therefore sufficient to implicate the endogenous opioid system in any physiologic process. Sawynok et al (1979) therefore suggested that a series of different methods should be employed to investigate this system, and only when all the criteria are met (Appendix A) can endogenous opioids be implicated in any process.

The findings of investigations which were performed to define the role of endogenous opioids during exercise will now be reviewed. In particular the evidence for the role that endogenous opioids may play in thermoregulation at rest and during exercise will be reviewed utilizing the criteria mentioned (Appendix A).

3.5 ENDOGENOUS OPIOIDS IN EXERCISE

Fraioli (1980) first reported a marked increase in peripheral blood levels of the endogenous opioid B-endorphin following a bout of physical exercise. This finding has been confirmed by numerous investigators (Harber et al , 1984) and presently it is well accepted that exercise can elevate serum concentrations of these substances up to five fold above basal concentrations (Harber et al , 1984). However, there is much debate and uncertainty about firstly the factors which influence the magnitude of rise of endogenous opioids during exercise and secondly the role that endogenous opioids play in exercise physiology. These two issues will now be discussed.

3.5.1 Factors affecting the magnitude of rise of plasma levels of endogenous opioids during exercise

3.5.1.1 Exercise intensity :

Colt et al (1981) first demonstrated that plasma B-endorphin immunoreactivity increases were higher in athletes following a "strenuous run" as compared to an "easy run". Although this finding appeared to link exercise intensity to rises in plasma B-endorphin immunoreactivity, Farrel et al (1982) showed that rises in plasma B-endorphin immunoreactivity were similar when athletes ran for 30 min at 60 % of their VO_2 max or at 80 % of their VO_2 max. Harber et al (1984) noted that these discrepant findings may have been the result of differences in experimental protocol between the two studies. These differences include exercise duration, subject numbers and the subjective assesment of exercise intensity used by Colt et al (1981).

Recent reports appear to confirm that exercise intensity above a critical point is necessary to significantly increase plasma B-endorphin immunoreactivity. De Meirleir et al (1986) have shown increases in plasma B-endorphin immunoreactivity only at exercise intensities sufficiently high to increase blood lactate levels above 4 $mmol.L^{-1}$. This has been confirmed by Mougin et al (1987).

Donevan et al (1987) concluded that an exercise intensity around 50-75 % of VO_2 max is necessary to cause a rise in plasma B-endorphin immunoreactivity (Fig 3.1). McMurray et al (1987) observed significant increases in plasma B-endorphin concentrations during exercise at 80% of VO_2 max but not at 60% or 40% of VO_2 max. Langenfeld et al (1987) observed no significant increase in plasma B-endorphin concentrations following 60 minutes of running or cycling at 60% of VO_2 max although there was a tendency to increased concentrations.

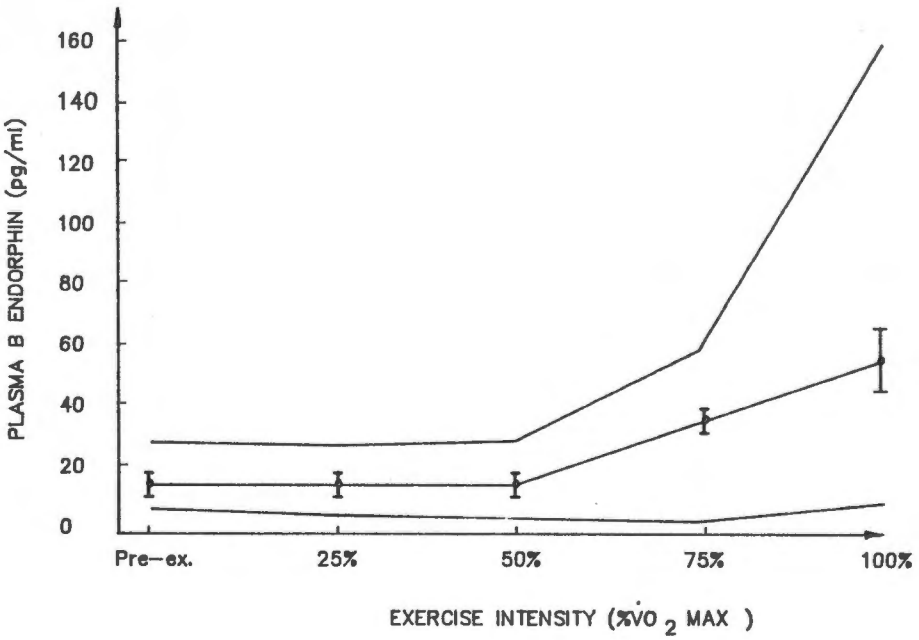

FIG 3.1 THE RELATIONSHIP BETWEEN EXERCISE INTENSITY (% $\dot{V}O_2$ MAX) AND PLASMA β – ENDORPHIN CONCENTRATION

AFTER DONEVAN ET AL (1987)

Rahkila et al (1987) concluded in their study that an anaerobic treadmill test and a maximal graded treadmill test but not running at submaximal intensity increases plasma B-endorphin levels. Farrel et al (1987) however observed no changes in plasma leucine-enkephalin levels at exercise intensities of 40%, 60% and 80% of VO_2 max. The evidence from these recent studies indicates that an exercise intensity of 60% to 80% of VO_2 max is probably required to increase plasma B-endorphin levels.

3.5.1.2 Exercise duration :

Very little data is available regarding the role of prolonged submaximal exercise on rises in B-endorphin immunoreactivity. Studies in which exercise protocols lasting longer than 30 minutes have been used (Bortz et al , 1981 ; Carr et al , 1981 ; Mougin et al , 1987) , indicate that prolonged exercise enhances plasma B-endorphin immunoreactivity (Francis , 1983). Comparison between these studies and interpretation of results is however difficult because exercise intensity levels were poorly documented.

Langenfeld et al (1987) demonstrated a trend towards an increase in plasma B-endorphin levels after 60 minutes cycling and running at 60% of VO_2 max but Kelso et al (1984) clearly showed an increased B-endorphin immunoreactivity following 120 min exercise at 50 % of VO_2max.

3.5.1.3 Endurance training :

Carr et al (1981) demonstrated that a two month endurance training program augmented the plasma B-endorphin immunoreactivity response to exercise. In addition endurance training appears to lower the resting plasma B-endorphin immunoreactivity (Lobstein et al , 1983 ; Carr et al , 1981). This finding appears to be consistent with the negative feedback mechanism proposed by Goldstein (1975) for narcotic addicts, who

have three times lower plasma B-endorphin immunoreactivity levels than normal subjects.

3.5.1.4 Sex :

Early studies comparing the plasma B-endorphin immunoreactivity responses to exercise in males and females, (Colt et al , 1981 ; Farrel et al , 1982 ; Gambert et al , 1981) have shown that males have a greater response than females. Two recent reports (McMurray et al , 1987 ; Rahkila et al , 1987) however failed to confirm the findings of these studies because similar responses are reported in both sexes.

3.5.1.5 Thermoregulatory stress :

In a single study by Kelso et al (1984) plasma B-endorphin immunoreactivity was documented during 120 min exercise at 50 % VO_2 max under three different conditions of thermoregulatory stress : Hot ($35^{o}C$, 50 % relative humidity), euhydrated (HE); Hot, dehydrated (HD) and Neutral ($24^{o}C$, 50 % relative humidity), euhydrated (NE). Plasma B-endorphin immunoreactivity increased after 120 min in all three trials but was significantly higher in the HE and HD trials than in the NE trial. The B-endorphin immunoreactivity response closely paralleled rectal temperature changes in all conditions.

3.5.2 The role of endogenous opioids in exercise physiology

The finding of exercise induced increases in plasma B-endorphin immunoreactivity has prompted several investigatiors to define its role in exercise physiology. However, several authors (Foley et al , 1979 ;Nakao et al , 1980) express some doubt that changes in plasma concentrations of endogenous opioids either influence or accurately reflect concentrations in the central nervous system where opioid action is known to occur. Evidence for rises in the central nervous system concentrations of endogenous

opioids in response to exercise has only been found in rats (Barta et al , 1981). It may however be possible that despite the fact that B-endorphins do not normally cross the blood brain barrier (Nakao et al , 1980), exercise may facilitate their entry into the brain by a mechanism similar to that demonstrated in rats injected with trypan blue dye (McArthur et al , 1985). These arguments are not based on sufficient facts and the doubt expressed by the above mentioned authors is justified.

The postulated roles of endogenous opioids in exercise have been reviewed thoroughly.(Harber et al , 1984 ; Farrel , 1982 ; Grossman et al , 1985 ; McArthur et al , 1985) and for the purposes of this discussion will only be summarized.

A detailed review on the role of endogenous opioids in thermoregulation will follow (Section 3.6).

3.5.2.1 Endogenous opioids and exercise induced euphoria (Runners high):

The speculation that elevated plasma B-endorphin immunoreactivity could be responsible for the positive mood changes associated with exercise (Bahrke et al , 1978 ;Yates et al , 1983), resulted in a number of studies being conducted in recent years to address this question. In these studies (Farrel et al , 1982 ;Markoff et al , 1982 ;Sutton et al , 1982) the Profile of Mood States (McNair et al , 1971) was administered before and after a bout of exercise. The findings in these studies of an improved mood state following exercise are not sufficient evidence that the rises in B-endorphin immunoreactivity were responsible for the improved mood. Furthermore the infusion of naloxone hydrochloride failed to block this tension reduction response to exercise (Markoff et al , 1982 ; Sutton et al , 1982). Thus Grossman et al (1984) suggested that mood state changes are not endorphin mediated. These findings may differ if different doses of naloxone are used (Haier et al , 1981 ; Sutton et al , 1982).

Morgan et al (1985) concluded that the endorphin hypothesis for exercise-induced euphoria remained unproven and required further investigation.

Two recent reports were unable to confirm the relationship between improved mood following exercise and raised plasma endogenous opioid levels. Goldfarb et al (1987) reported a significant increase in plasma B-endorphin level following a maximal graded cycle ergometer test. However, no change was observed in the Multiple Affect Adjective check list following exercise (Zuckerman et al , 1965). Farrel et al (1987) were unable to document a relationship between the Profile of Mood States assessment and plasma leucine enkephalin-like peptides after three submaximal exercise tests. They conclude that psychological alterations which occur during exercise are not related to plasma leucine enkephalin levels.

The evidence to date is sufficient to conclude that rises in plasma levels of endogenous opioids in response to physical exertion are not related to alterations im mood induced by exercise. This however does not mean that endogenous opioid concentrations in central nervous system tissue do not change during exercise which could result in alterations of the mood state of the individual.

3.5.2.2 Endogenous opioids and altered pain perception during exercise

Berk et al (1981) suggested that endorphins may provide analgesia against pain producing catabolites generated during exercise. Haier et al (1981) demonstrated that running one mile significantly lengthened the time it took to report pain from a 3 pound weight resting on a fingertip. Naloxone (10 mg) completely blocked this exercise - induced analgesia whereas 2 mg naloxone provided more analgesia, again demonstrating the dose dependent effect of naloxone. At present if appears that endorphins may

produce some analgesia during an exercise bout but this requires further investigation to confirm.

3.5.2.3 Endogenous opioids and reproducive dysfunction in endurance trained females

The reproductive disturbances (delay in menarche, dysfunctional uterine bleeding; secondary amenorrhea and inadequacy of the luteal phase) reported in female athletes with increasing frequency have been well documented (Baker et al , 1981 ; Bonen et al , 1979 ; Frisch et al , 1980 ; Shangold et al , 1979 ; Noakes et al , 1988). A detailed discussion of these disturbances is beyond the scope of this presentation and only the possible link between endogenous opioids and these disturbances will be discussed. The subject has been reviewed recently (McArthur , 1985 ; Harber et al , 1984). The main thrust of the argument implicating endogenous opioids as an aetiological factor in these disturbances appears to be the fact that opioids inhibit pituitary luteinising hormone release (Harber et al , 1984). This is confirmed by the demonstration that naloxone administration increases luteinising hormone secretion in the late follicular and mid luteal phases of the menstrual cycle (Blankstein et al , 1981 ; Quigley et al , 1980 ; Wildt et al , 1981).

However doubt has been expressed as to firstly whether the 2 to 3 fold increase in plasma B-endorphin levels demonstrated in female athletes (Harber et al , 1984) is enough to exert an inhibitory effect upon luteinizing hormone secretion (McArthur , 1985) and secondly whether increases in plasma concentration of B-endorphin during exercise reflect changes in the hypothalamus and pituitary where luteinizing hormone release is controlled (McArthur , 1985).

Two further arguments against endogenous opioids as the only cause for reproductive dysfunction are firstly that there appears

to be little agreement regarding the changes in gonadotrophin concentration in response to chronic exercise (Harber et al , 1984), and secondly that there are many other possible causes for this observed reproductive dysfunction in female athletes. These include the percentage body fat hypothesis, late menarche, previous menstrual irregularities, an immature reproductive endocrine axis, intense training, psychological stress and diet (Noakes et al , 1988).

3.5.2.4 Endogenous opioids and the response of the stress hormones during exercise

i) Adrenocorticotrophic hormone (ACTH)

It is well documented that plasma levels of both ACTH and B-endorphin increase in response to exercise (De Meirleir et al , 1986 ; Fraioli et al , 1980). There is evidence that opioids modulate ACTH secretion because naloxone administration elevates circulating ACTH levels (Blankstein et al , 1980 ; Volavka et al , 1979) whereas opioid peptides suppress the pituitary-adrenal axis (Delitala et al , 1981a ; Delitala et al 1981b ; Stubbs et al , 1978) causing a decrease in circulating ACTH levels. It therefore appears that endogenous opioids may play a role in the ACTH response to exercise stress.

ii) Growth hormone (GH) and Prolactin

Plasma growth hormone and prolactin levels increase in response to exercise. The increase in growth hormone levels are exaggerated during high intensity exercise and in untrained subjects (Shephard , 1985). The effect of varying doses of naloxone administration on the GH and prolactin response to exercise has been studied extensively (Spiler et al , 1980 ; Sutton et al , 1982 ; Mayer et al , 1980 ; Moretti et al , 1983 ; Grossman et al , 1984). Because of conflicting findings in

these studies, no firm conclusions can be made regarding opioids and GH and prolactin release during exercise.

iii) Other hormones

The increase in plasma catecholamines, plasma renin activity and serum aldosterone levels in response to exercise is also altered by naloxone administration (Grossman et al , 1984). It is concluded in that study that there may be direct opiate modulation of the sympathetic nervous system and the adrenal medulla.

3.5.2.5 Endogenous opioids and the cardiorespiratory response to exercise

Most studies indicate that endogenous opioids do not play a role in the cardiovascular response to exercise (Grossman et al , 1984 ; Willer et al , 1978 ; Staessen et al , 1985). These are however isolated reports of a possible peripheral vasodilatory role of circulating endogenous opioids (Altura et al , 1980 ; Lin et al , 1980 ; Wong et al , 1981). Opioids may also be involved in the maintenance of normal blood pressure at rest (Copolov et al , 1983 ; Rubin , 1984).

A recent report (Grossman et al , 1984) indicated that opioid antagonism significantly increased ventilation during exercise both by increasing respiratory rate and tidal volume. It was concluded from that study that endogenous opioids may play a role in ventilatory regulation during exercise.

3.6 ENDOGENOUS OPIOIDS AND THERMOREGULATION

Over the past two decades considerable evidence has accumulated to support the hypothesis that endogenous opioids play a role in thermoregulation at rest. However very little data are available

on the role of endogenous opioids in thermoregulation during exercise. Sawynok et al (1979), proposed a series of criteria (Appendix A) which, when fullfilled, would indicate very strongly that the endogenous opioid system mediates a particular physiological or pharmacological response. It is in the light of these criteria that evidence for the role of endogenous opioids in thermoregulation at rest and during exercise, will be reviewed.

3.6.1 Endogenous opioids and thermoregulation at rest

Most of the research on opioids and thermoregulation has been conducted on the animal model in the resting state. A number of methods of investigation have been employed and the findings of these will now be reviewed.

3.6.1.1 The thermoregulatory response to administration of exogenous opiates

This appears to be the most common method of investigation used and the results of recent studies are summarized in Table 3.3. It is immediately obvious that the core temperature response to exogenous opioid administration varies and can either increase, exhibit no change or decrease. These discrepancies can however be explained by analysing factors that may affect the core temperature response to opiate administration. These factors include the ambient temperature, the dose of opiate used, the route of administration of the opiate, the site of temperature measurement and the type of opiate used. In the subsequent discussion the reader is asked to refer to studies listed alphabetically in Table 3.3.

i) Ambient temperature

In a neutral ambient temperature (20-25^{o}C), low doses of B-endorphin (5 ug) administered intraventricularly (usually the

TABLE 3.3

THE THERMOREGULATORY RESPONSE TO THE ADMINISTRATION OF EXOGENOUS OPIODS AT REST

STUDY	ANIMAL MODEL	OPIOID TYPE	OPIOID DOSE	ROUTE OF ADMINISTRATION	SITE OF TEMPERATURE MEASUREMENT	EFFECT ON CORE TEMPERATURE	AMBIENT TEMPERATURE	REFERENCE
A	Rabbits	B-endorphin	5ug	Preoptic/Anterior hypothalamic	Brain	Slight increase	2°C	Rezvani et al (1982)
B	Rabbits	B-endorphin	5ug	Preoptic/Anterior hypothalamic	Brain	Increase	27°C	Rezvani et al (1982)
C	Rats	B-endorphin	5ug	Intraventricular (3rd Ventricle)	Rectal	No change	22,5-25°C	Holaday et al (1977)
D	Rats	Morphine	15ug	Intraventricular (3rd Ventricle)	Rectal	Increase	22,5-25°C	Holaday et al (1977)
E	Rats	Morphine	10mg/kg	Subcutaneous	Rectal	Increase	22-23°C	Holaday et al (1977)
F	Rats	B-endorphin	5-10ug	Intraventricular (3rd Ventricle)	Rectal	Decrease	23°C	Holaday et al (1977)
G	Rats	B-endorphin	7,5ug	Intraventricular (3rd Ventricle)	Rectal	No change	26-27°C	Holaday et al (1978a)
H	Rats	B-endorphin	7,5ug	Intraventricular (3rd Ventricle)	Rectal	Increase	34,5°C	Holaday et al (1978a)
I	Rats	B-endorphin	30ug	Intraventricular (3rd Ventricle)	Rectal	Decrease	27°C	Holaday et al (1978a)

third ventricle of the brain) can either cause an increase (study B, Table 3.3) or a decrease in rectal temperature (study F, Table 3.3). Studies A and B (Table 3.3) demonstrate that the increase in rectal temperature, following the administration of low dose (5 ug) B-endorphin into the pre-optic/anterior hypothalamic area, is much less when the rabbits are exposed to cold (2^{o}C) as opposed to neutral (27 ^{o}C) ambient temperatures. Studies G and H (Table 3.3) clearly show that in hot (34,5 ^{o}C) ambient temperatures the rectal temperature response is much higher than under neutral conditions.

In summary the data indicate firstly that ambient temperatures influence the rise in rectal temperature caused by low dose opioid administration and secondly that higher temperatures augment this response. In neutral ambient temperatures, however, the results are conflicting.

ii) The dose of opiate administered

Studies G and I (Table 3.3) clearly indicate that low dose (7,5 ug) intraventricular administration of B-endorphin resulted in little change in rectal temperature, whereas high dose (30 ug) B-endorphin caused a decrease in rectal temperature.

iii) Route of administration and site of temperature measurement

When comparing studies B and C (Table 3.3) it is noted that the administration of 5 ug B-endorphin does not elicit similar responses in core temperature. These differences may be the result of either different routes of administration (Pre-optic/anterior hypothalamic vs intraventicular) or because core temperature was measured at different sites (brain vs rectum).

iv) Type of opiate used

The differences in rectal temperature response observed in studies C and D (Table 3.3) could be attributed to the different opiates used based on the assumption that B-endorphin is roughly three times more potent than morphine, and morphine was therefore administered at three times the dose of B-endorphin. However the accuracy of this assumption is questionable.

It must be noted that studies by Holaday et al (1978a and 1978b) clearly indicate that normal hypothalamic - pituitary - adrenal function is essential to demonstrate these rectal temperature responses to exogenous opiate administration.

3.6.1.2 The thermoregulatory response to opioid receptor antagonism by naloxone hydrochloride

A number of investigators have reported the effects of naloxone administration on core temperature at rest (Table 3.4). As in the case of opiate administration the core temperature response to naloxone administration is influenced by a number of factors. The reader is again asked to refer to the alphabetically listed studies in Table 3.4.

i) Ambient temperature

Studies B* and D (Table 3.4) show that the subcutaneous administration of very high doses (10 $mg.kg^{-1}$) of naloxone hydrochloride to rats decreased the resting rectal temperature in neutral ambient conditions (23^{o}C), whereas rectal temperature increased in hot ambient conditions (34,5^{o}C) following naloxone injection. In neutral ambient conditions high dose (10mg) naloxone administered to human subjects also decreased resting rectal temperature (study I, Table 3.4). This finding cannot be compared to the other studies A to D (Table 3.4) as a number of

TABLE 3.4

THE THERMOREGULATORY RESPONSE TO THE ADMINISTRATION OF NALOXONE HYDROCHLORIDE AT REST

STUDY	ANIMALS	NALOXONE DOSE	ROUTE OF ADMINISTRATION	AMBIENT TEMPERATURE	EFFECT ON CORE TEMPERATURE	REFERENCE
A	Rats	10mg/kg	Intraperitoneal	36,6°C	Slight Increase	Holaday et al (1978b)
B	Rats	10mg/kg	Intraperitoneal	34,5°C	Increase	Holaday et al (1978b)
C	Rabbits	5ug	Preoptic/Anterior hypothalamic	27°C	No change	Rezvani et al (1982)
D	Rats	10mg/kg	Subcutaneous	23°C	Decrease	Goldstein (1975)
E	Rats	2,5mg/kg	?	?	Slight decrease	Stewardt et al (1979)
F	Rats	10mg/kg	?	?	Decrease (marked)	Stewart et al (1979)
G	Rats (stressed)	2,5mg/kg	?	?	Slight decrease	Stewart et al (1979)
H	Rats (stressed)	10mg/kg	?	?	No change	Stewart et al (1979)
I	Humans	10mg	Intravenous	18-22°C	Decrease	Staessen et al (1985)

variables differ including the subjects, the naloxone dose and the route of administration.

ii) Dose of naloxone

It is well documented that different doses of naloxone can elicit different responses in a variety of physiologic processes (Section 3.4). Studies E and F demonstrate that 2mg.kg^{-1} and 10 mg.kg^{-1} naloxone administered to rats elicit different rectal temperature responses. This is also confirmed by the results of studies G and H (Table 3.4). When comparing studies C and D (Table 3.4) it is possible that either the dose of naloxone used (5ug vs 10 mg.kg^{-1}) or the route of administration (Pre-optic /anterior hypothalamic vs subcutaneous) could account for the different rectal temperature responses. In studies E, F, G and H (Table 3.4) the route of administration as well as the ambient temperature were not indicated but are assumed to be the same in all the studies.

iii) Psychological stress

In studies E and G as well as F and H (Table 3.4) the rectal temperature response after naloxone administration unstressed and stressed rats is documented. The hypothermic effect of naloxone appears to be attenuated by psychological stress. Stewart et al (1979) have also shown that stress produces a hyperthermia which is attenuated by naloxone administration. It is postulated that stress induced increases in pituitary B-endorphin act on thermoregulatory control centres in the central nervous system to raise core temperature.

iv) Route of administration

As mentioned previously the different rectal temperature responses elicited in studies C and D (Table 3.4) could be as a

result of either different naloxone doses or different routes of administration of naloxone.

3.6.1.3 Evidence that other opioid antagonists produce the same effect as naloxone

Nalorphine, another opiate antagonist which is less specific that naloxone, has been shown to produce a similar mild hyperthermic response as naloxone when injected at neutral ambient temperatures. (Lotti et al , 1965a ; Lotti et al , 1965b ; Ary et al , 1976)

3.6.1.4 Evidence that isomers of antagonists which lack opiate antagonist activity, for example dextrallorphan, are inactive

In a single report by Goldstein et al (1975) dextrallorphan, the inert enantiomer of the antagonist levallorphan, produced a similar response in rectal temperature to saline injection, which was opposite to that elicited by naloxone.

3.6.1.5 Evidence of a direct release of endogenous opioids by the stimulus, for example heat

Blasig et al (1978) have demonstrated a seven- to eightfold elevation in plasma B-endorphin levels in response to stress induced hyperthermia and this response is markedly reduced by naloxone administation.

It appears that no studies have been reported to show that agents which inhibit the breakdown of endogenous opioids potentiate a naloxone-antagonized thermoregulatory response. However as there appears to be sufficient evidence to fullfill most of the criteria proposed by Sawynok et al (1979) (Appendix A), it is concluded that endogenous opioids play a role in thermoregulation at rest. The next step is to address to possible mechanisms by

which endogenous opioids may influence temperature control at rest.

3.6.1.6 The mechanisms by which endogenous opioids may influence temperature regulation at rest

The data presented so far has shown that in most of the studies low dose B-endorphin injection into the brain causes hyperthermia (Studies B,C,D,F,G,H Table 3.3). In addition naloxone injection under neutral environmental conditions appears to decrease core temperature (Studies D and E, Table 3.4). It appears therefore that opioids increase core temperature at rest. The mechanisms responsible for this increase could either be an increased rate of heat production or a decreased rate of heat loss. Rezvani et al (1982) showed very neatly that B-endorphin injected into the pre-optic/anterior hypothalamic area of rabbits did not affect the metabolic rate. In addition their study indicated that following B-endorphin administration the posture of the rabbits changed from heat dissipating to heat conserving patterns and peripheral vasoconstriction occurred. Evaporative heat loss was also diminished. This study therefore indicates that endogenous opioids tend to activate heat conserving mechanisms. This activation could be because endogenous opioids either reduce the responsiveness of neurons to heat stimuli (Calvillo et al , 1979 ; Gordon et al , 1981) or lower the central hypothalamic thermostat (Holaday et al , 1978b).

In conclusion, it appears that endogenous opioids play a role in thermoregulation in the resting animal by activating heat conserving mechanisms.

3.6.2 Endogenous opioids and thermoregulation during exercise

Endogenous opioids appear to play a role in thermorgulation at rest but few data are available on their role in thermoregulation during exercise. The evidence available at present linking the

opioid response during exercise to thermoregulation during exercise will now be reviewed.

Kelso et al (1983) observed an exaggerated B-endorphin response to exercise in hyperthermic (32°C, 50 % relative humidity) conditions than in normothermic conditions. The subjects exercised at 60 % at their $\dot{V}O_2$ max for a duration of 60 min . These differences, however, were not statistically significant ($p>0,05$). A year later Kelso et al (1984) reported significantly higher B-endorphin levels in subjects performing exercise in conditions of thermoregulatory stress. The B-endorphin response to exercise was measured during 120 min of exercise at 50 % of $\dot{V}O_2$ max under three conditions: Neutral (24°C, 50 % relative humidity) - euhydration (NE); Hot (35°C, 50 % relative humidity) - euhydration (HE) and Hot dehydration (HD). Their results show that exercise in the HD and the HE conditions resulted in significantly ($P<0,05$) elevated levels of plasma B-endorphin above those observed in NE. Calculated changes in plasma volume did not account for these findings. Furthermore, the rises in B-endorphin levels closely parallelled the rises in rectal temperature in all conditions.

It must however be stated that the authors do not comment on the fact that it was either the thermoregulatory stress that caused the rise in B-endorphin levels or that exercise induced rises in B-endorphin contributed to the increase in thermoregulatory stress. The latter possibility must be considered particularly in the light of the conclusions reached on the role of endogenous opioids in thermoregulation at rest (Opioid induced heat conserving behaviour at rest : Section 3.6.1). Furthermore, no comment was made on the subjects relative fitness levels (average $\dot{V}O_2$ max indicated as 48,5 8,0 $ml.kg^{-1}\ min^{-1}$) and state of heat acclimatization, both factors which may influence the interpretation of these findings.

If it is assumed that the release of B-endorphin during exercise is a factor which plays a role in heat conservation during exercise (consistent with conclusions reached in Section 3.6.1), the core temperature response of the endurance trained athlete, with his augmented B-endorphin response would be very high. The contrary is however observed (Lobstein et al , 1983), which raises the intriguing possibility that the augmented B-endorphin response as a result of training, could lead to the development of tolerance, and cause blunting of B-endorphin induced heat conserving mechanisms. The result would then be a lower core temperature during exercise in the endurance trained athlete. Although there is no evidence of this at present a similar mechanism may occur during heat acclimatization.

The only other study adressing the possible role of endogenous opioids in exercise thermoregulation is that of De Meirleir et al (1985). In that study, 2 mg intravenous naloxone hydrochloride completely abolished the rise in sublingual temperature during maximal exercise. The ambient temperature was 20^{o}C and relative humidity 60 %. These results (Table 3.5) would certainly indicate that the release of B-endorphin during exercise plays some role in maintaining body temperature during exercise (heat conservation) and this is consistent with the conclusions reached in Section 3.6.1. It must however be stated that sublingual temperature is a poor indicator of core temperature unless measured meticulously (Mairiaux et al , 1983 : Nichols et al , 1972). It is of particular concern that the exact methodology used in the measurement of sublingual temperature in this study was not described.

TABLE 3.5

THE SUBLINGUAL THEMPERATURES (MEANS IN ^{O}C) BEFORE, IMMEDIATELY AFTER, AND ONE HOUR AFTER EXERCISE IN 10 HEALTHY MEN GIVEN PLACEBO OR 2 MG NALOXONE FIVE MINUTES BEFORE EXERCISE

	CONTROL	PLACEBO	NALOXONE
Before exercise	36,85	36,64	36,58
Inmediately after	37,33	37,16	36,40 *
One hour after	36,83	36,67	36,34 *

* p<0,001 compared to control and placebo studies

Adapted from De Meirleir et al (1985)

3.7 SUMMARY

The evidence, as presented above, implicating endogenous opioids in thermoregulatory control during exercise is certainly not sufficient particularly in the light of the criteria proposed by Sawynok et al (1979) (Appendix A). It is also clear that further investigation is required to define the possible role of the endogenous opioid system in thermoregulation during exercise. Such a study would have to be conducted in stages to accommodate variables such as environmental conditions, state of training and acclimatization of the subjects, exercise intensity, exercise duration, type of exercise and also the site of core temperature measurement.

A useful cost effective starting point for such investigations would be to study the effects of different doses of the opioid receptor antagonist naloxone hydrochloride on the thermoregulatory response to exercise. In addition such investigations could incorporate different exercise intensities and duration, and body core temperature could be measured at different sites.

CHAPTER FOUR

THE EFFECT OF NALOXONE ADMINISTRATION ON THE THERMOREGULATORY RESPONSE DURING EXERCISE : METHODS AND RESULTS

4.1 INTRODUCTION

At present there is reasonable evidence to suggest that the endogenous opioid system plays a role in maintaining normothermia in animals at rest. (Section 3.6.1) However, the evidence that endogenous opioids play a role in thermoregulatory responses during exercise, is less conclusive and requires further investigation (Section 3.6.2). A number of methods can be employed to investigate the endogenous opioid system. The observed response to naloxone antagonism appears to be particularly appropriate as a screening and investigative tool in studies on thermoregulatory responses. (Section 3.4)

A survey of the existing literature indicates that a number of variables must be taken into consideration when conducting an investigation into the role of endogenous opioids in thermoregulation during exercise.

These variables include:

i) Naloxone dose administered (Section 3.6.1.2)

ii) Exercise intensity (Section 3.5.1.1)

iii) Exercise duration (Section 3.5.1.2)

iv) The site of core temperature measurement (Section 3.6.1.1)

v) Ambient environmental conditions (Section 3.6.1.1)

vi) State of physical conditioning of the subjects (Section 3.5.1.3)

vii) State of heat acclimatization of the subjects (Section 2.3)

It is clear that, in order to investigate the thermoregulatory response to naloxone administration, a number of different studies would have to be conducted to incorporate all these variables.

This study was designed to observe thermoregulatory responses during exercise following naloxone administration. It was conducted in two parts so that the effect of a number of the above mentioned variables could be studied. In both studies the subjects were not heat acclimatized but they were physically conditioned. Ambient conditions were neutral in both studies. The effect of these variables where therefore not studied.

Part I of the study was conducted in order to observe the thermoregulatory responses during exercise following the administration of two different doses of naloxone. Furthermore, subjects exercised at a moderate intensity for a prolonged period.

Part II of the study was designed to observe thermoregulatory responses during high intensity, short duration exercise. In addition, temperature measurements were made at different body sites.

The observations made during these studies would therefore provide valuable information on the role of endogenous opioids in exercise thermoregulation specifically examining variables such as naloxone dose , exercise intensity and duration as well as the site of core temperature measurement.

The methods, statistical analysis and results of Part I and Part II will now be discussed.

4.2 PART I : THE EFFECT OF NALOXONE ADMINISTRATION ON THERMOREGULATORY RESPONSES DURING PROLONGED SUBMAXIMAL EXERCISE

4.2.1 Methods

4.2.1.1 Subjects

Nine healthy men who participated in endurance exercise on a regular basis served as subjects. All were volunteers who gave their informed consent. The physical characteristics of the subjects are listed in Table 4.1. The subjects maintained their normal level of physical activity during the course of the study, with the exception that strenuous exercise was not performed on the day before experimental sessions.

TABLE 4.1

PHYSICAL CHARACTERISTICS OF THE SUBJECTS (N=9)

Age (Years)	23,4 ± 1,1
Height (cm)	178 ± 1
Body Weight (kg)	75,5 ± 2,7
Maximum oxygen uptake ($ml.kg^{-1}.min^{-1}$)	52,5 ± 2,6
Maximum heart rate ($beats.min^{-1}$)	190 ± 4

Values are mean ± SE

4.2.1.2 Measurement of respiratory variables, maximum oxygen uptake ($\dot{V}O_2$ max) and maximum heart rate (HR max).

Prior to commencement of the thermoregulatory investigation, all subjects performed a maximal graded exercise test on a Monark cycle ergometer. The starting work rate was 60W and was incremented by 30 Watts every two minutes until volitional exhaustion. The subjects breathed through a low-resistance Hans Rudolph valve and the relevant respiratory variables were determined over each 20 sec exercise period using automated open-circuit spirometry (Gould 9 000 IV Computerized Pulmonary Lab). The system's dry rolling seal spirometer, paramagnetic O_2 analyser and infrared absorption CO_2 analyser were calibrated immediately before and after each test using standard procedures. Heart rate (HR) was calculated from electrocardiographic tracings (CM5 placement) obtained during the final 15 sec of each workload. The peak HR and $\dot{V}O_2$ attained during graded exercise testing were taken as HR max and $\dot{V}O_2$ max respectively.

4.2.1.3 Measurement of thermoregulatory responses

The thermoregulatory study was conducted in a randomized double-blind crossover fashion. On each of three experimental days, at least 1 week apart, subjects received volume - matched intravenous infusions containing either a placebo (0,9 % saline), 2 mg naloxone (Narcan) or 10 mg naloxone. The 2 mg dose was chosen firstly because this dose appears to exert a profound effect on exercise thermoregulation (De Meirleir et al , 1985), and secondly because it represents a low dose. The 10 mg dose was chosen because it represents a high dose of naloxone (Section 3.4) and has also been reported to elicit different effects compared to low dose naloxone in a variety of physiological processes (Haier et al , 1981). The drugs were infused intravenously over 5 min.

Testing was conducted in an environmentally controlled laboratory with a dry bulb temperature of 19-21^{o}C and relative humidity of 45-55 %. On the 3 experimental days, subjects reported to the laboratory at the same time of day having avoided meals, fluids (with the exception of water which was consumed ad libitum) and cigarettes for at least 3 hours. Subjects were acclimated to the ambient conditions for 30 min prior to receiving that days infusion. Within 5 min of the completion of their infusion, subjects were seated on a calibrated Monark cycle ergometer. After 5 min of seated rest, during which time resting observations were made, subjects performed 30 min cycling. The duration of exercise was chosen as 30 min because it has been shown that rectal temperature responses to steady state submaximal exercise stabilize at 30 min (Nielsen et al, 1938) Furthermore the reported serum half life of naloxone is reported as 60 min (Ngai et al , 1976). As naloxone was infused 15 min prior to exercise, the 30 min exercise period would ensure that adequate blood concentrations of naloxone were present at the end of exercise. Individual work rates were chosen to elicit 70 % of the HR max attained during graded exercise testing. These work rates remained constant for all three pharmacologic interventions. During the exercise test no fluids were consumed and only athletic shorts and shoes were worn.

The rectal temperature was measured with a copper-constantan thermocouple inserted to a depth of 10 cm from the external anal sphincter. Thermoelectric voltages were measured on a precision vernier potentiometer at the end of each min during rest (5 min), exercise (30 min) and recovery (5 min). The thermocouples were calibrated in stirred water baths against a certified thermometer on completion of the study. Heart rate (from electrocardiographic tracings) and blood pressure (auscultatory technique) were determined immediately before exercise and at 15 min and 30 min of exercise. Each participant's subjective perception of effort was evaluated using the Borg 6 to 20 perceived exertion scale (Borg et al , 1970), at 15 and 30 min of

exercise. On completion of the initial 15 min of exercise, respiratory variables were measured over a 5 min period, as outlined earlier. Subjects were weighed in the nude before and after exercise on a calibrated electronic scale sensitive to a change of 25 g and water losses were estimated from weight differences. This excludes weight loss from metabolic fuel utilization which is assumed to be minimal. This value would also not likely differ between interventions.

4.2.2 Statistical analysis

Significance of difference between experimental variables was assessed using analysis of variance for repeated measures and paired t-tests, where appropriate. Statistical significance was established at $p<0,05$.

4.2.3 Results

4.2.3.1 Cardiorespiratory response and perception of effort

The effect of 2 mg and 10 mg naloxone on the cardiorespiratory response to 30 min cycling is documented in Table 4.2. In agreement with previous research (Grossman et al , 1984 ; Willer et al , 1978 ; Staessen et al , 1985), analysis of variance did not reveal a significant effect of naloxone on any of the measured cardiorespiratory responses. Likewise, Borg ratings of perceived exertion were similar for placebo, 2 mg naloxone and 10 mg naloxone (Table 4.2)

4.2.3.2 Thermoregulatory responses

The effect of 2 mg and 10 mg naloxone on resting, exercise and recovery rectal temperatures is depicted in Fig 4.1. Resting rectal temperatures were similar for placebo (37,23 ± 0.07 ^{o}C, at 0 min), 2 mg naloxone (37,22 ± 0,06^{o}C at 0 min) and 10 mg naloxone (37,32 ± 0,08^{o}C at 0 min). Likewise analysis of

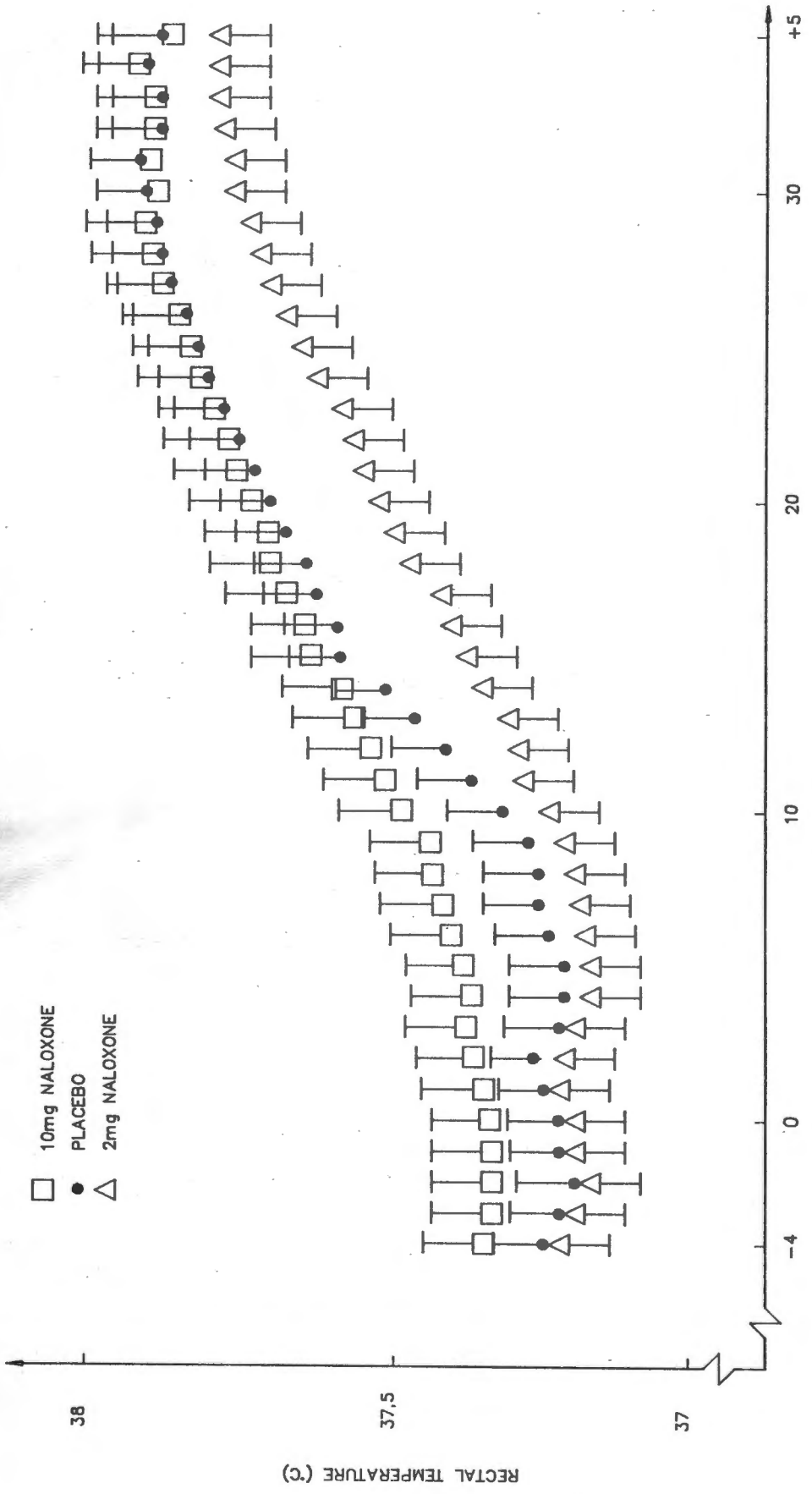

FIG 4.1 THE EFFECT OF TWO DOSES NALOXONE (2mg AND 10mg) ON RECTAL TEMPERATURE DURING SUBMAXIMAL EXERCISE

ADDENDUM TO FIG 4.1

THE THERMOREGULATORY RESPONSE TO SUBMAXIMAL EXERCISE AFTER THE ADMINISTRATION OF PLACEBO, 2MG AND 10MG NALOXONE (VALUES ARE MEAN ± SE IN °C)

TIME	PLACEBO	2MG	10MG
-4	37.25 ± 0.08	37.22 ± 0.08	37.35 ± 0.10
0	37.22 ± 0.09	37.18 ± 0.08	37.34 ± 0.09
5	37.22 ± 0.09	37.16 ± 0.08	37.38 ± 0.09
10	37.32 ± 0.09	37.24 ± 0.09	37.49 ± 0.10
15	37.59 ± 0.09	37.37 ± 0.08	37.64 ± 0.10
20	37.71 ± 0.08	37.52 ± 0.09	37.74 ± 0.09
25	37.83 ± 0.08	37.65 ± 0.09	37.84 ± 0.10
30	37.91 ± 0.09	37.76 ± 0.09	37.90 ± 0.10

TABLE 4.2

THE EFFECT OF 2 MG AND 10 MG NALOXONE ON THE CARDIORESPIRATORY RESPONSE TO SUBMAXIMAL EXERCISE (PART I)

	PLACEBO	2 MG NALOXONE	10 MG NALOXONE
HR (beats.min $^{-1}$)	135 ± 6	133 ± 6	134 ± 5
SBP (mmHg)	161 ± 3	160 ± 4	164 ± 5
DBP (mmHg)	58 ± 5	62 ± 5	55 ± 4
HR (% HR max)	71 ± 3	71 ± 3	71 ± 3
Respiratory rate (breaths.min $^{-1}$)	27 ± 1	25 ± 2	26 ± 2
VE (1.min $^{-1}$)	58,8 ± 1,8	57,6 ± 1,7	56,7 ± 2,1
$\dot{V}O_2$ (1.min $^{-1}$)	2,09 ± 0,08	2,14 ± 0,10	2,10 ± 0,10
$\dot{V}O_2$ (ml.kg^{-1}.min^{-1})	28,0 ± 1,6	28,6 ± 1,8	28,2 ± 1,9
$\dot{V}O_2$ (% VO_2 max)	54 ± 2	55 ± 2	54 ± 2
$\dot{V}CO_2$ (1.min^{-1})	1,98 ± 0,09	2,02 ± 0,09	1,98 ± 0,10
RER	0,95 ± 0,01	0,95 ± 0,01	0,94 ± 0,01

Values are mean ± SE; n = 9. HR = Heart rate; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; VE = Pulmonary minute ventilation; $\dot{V}O_2$ = Oxygen uptake; $\dot{V}O_2$ max = Maximal oxygen uptake; $\dot{V}CO_2$ = Carbon dioxide output; REF = Respiratory exchange ratio.

Values did not differ significantly

variance failed to demonstrate a significant effect of either dose of naloxone on the rectal temperature response during exercise or during 5 min of recovery. Thus the rise in rectal temperature evoked by 30 min cycling at a fixed submaximal exercise intensity was essentially equivalent for placebo (0,69 ± 0,04°C increase from 0 to 30 min, $p<0,001$), 2 mg naloxone (0,60 ± 0,04°C increase from 0 to 30 min, $p<0,001$) and 10 mg naloxone (0,60 ± 0,04°C increase from 0 to 30 min, $p<0,001$).

As was the case for rectal temperature, the calculated total water loss during exercise for placebo (269 + 19 ml) was not significantly altered by the infusion of 2 mg (256 + 19 ml) or 10 mg (269 + 15 ml) naloxone.

4.3 PART II : THE EFFECT OF NALOXONE ADMINISTRATION ON OESOPHAGEAL, RECTAL AND SUBLINGUAL TEMPERATURE DURING MAXIMAL EXERCISE

4.3.1 Methods

4.3.1.1 Subjects

Eight healthy male competitive cyclists acted as subjects. Their physical characteristics are listed in Table 4.3. All were volunteers and written informed consent was obtained for the study. Subjects maintained their normal level of physical activity during the course of the study with the exception that strenuous exercise was not performed on the day before experimental days.

4.3.1.2 Drug infusion

The study was conducted in a randomized double blind crossover fashion. On two experimental days at least 1 week apart, subjects received volume - matched infusions containing either 2 mg of naloxone hydrochloride (Narcan) or placebo (0,09 % saline).

TABLE 4.3

PHYSICAL CHARACTERISTICS OF THE SUBJECTS (N = 8)

Age (Years)	23,5 ± 2,1
Height (cm)	178 ± 1
Body Weight (kg)	69,5 ± 5,9
Maximum oxygen uptake ($ml.kg^{-1}.min^{-1}$)	62,8 ± 6,5

Values are mean ± SE

The 2 mg dose was chozen on the basis i) that this was the dose used in the study by De Meirleir et al (1985) and ii) that there was no significant difference in rectal temperature response during submaximal exercise with infusion of either 2 mg or 10 mg naloxone.

Naloxone and placebo were infused intravenously over 2 min. The shorter infusion time was chosen as it was established in Part I of the study that the subjects could tolerate rapid infusion well. The volume of the infusate was also much less in Part II (5ml) than in Part I (25ml). A rapid infusion time allowed more time to prepare the subject for the exercise test.

4.3.1.3 Graded exercise testing

The experiments were conducted in an enviromentally controlled laboratory with a dry bulb temperature of 21^{o}C and a relative humidity of 55 %. On each of the two experimental days the subjects reported to the laboratory at the same time of the day, having avoided meals and fluids, with the exception of water, for at least 3 hours. The subjects were acclimated to the ambient conditions for 30 min prior to receiving that day's intravenous infusion. Within 6 min of the completion of the intravenous infusion, subjects commenced a maximal graded exercise test on a calibrated Monark cycle ergometer at a work rate of 80 Watts, the pedal frequency being 80 rpm. The pedal frequency remained constant and the work rate was incremented by 40 Watts every three minutes until the pedal frequency could no longer be maintained.

4.3.1.4 Physiological measurements

The oesophageal (Toes), rectal (Tre) and sublingual (Tsl) temperatures were recorded at 1 min intervals during the 5 min period after infusion and also during the initial 8 minutes period of recovery. During exercise Toes was recorded on

completion of each workload. Toes was measured at the level of the heart using the electrocardiographic method of Brengelmann et al (1979). Tre was measured 10cm beyond the external anal sphincter and Tsl was measured under the tongue. Although the subjects were strongly encouraged to keep their mouths closed for Tsl measurements, they were often unable to do so during the first 2 min of recovery.

Copper-constantan thermocouples were used for all temperature measurements, and thermoelectric voltages were recorded on a precision vernier potentiometer. The thermocouples were calibrated simultaneously in a stirred water bath against a certified thermometer on completion of the study. During the exercise test the subjects breathed through a low resistance Hans-Rudolph valve and the relevant respiratory variables were determined each minute of exercise using automated open circuit spiromtery (Gould 9 000 IV Computerized Pulmonary Lab).

The system's dry rolling seal spirometer, paramagnetic O_2 analyser and infrared absorbtion CO_2 analyser were calibrated immediately before each test using standard procedures. The heart rates were calculated from electrocardiographic tracings (CM5 placement) obtained during the final 15 seconds of each workload. The peak heart rate and O_2 uptake attained during graded exercise testing were taken as the maximal heart rate and maximal O_2 uptake respectively.

4.3.2 Statistical analysis

Significance of difference between experimental variables was asessed using analysis of variance for repeated measures and paired t-test where appropriate. Statistical significance was established at $p<0,05$.

4.3.3 Results

The effect of 2 mg naloxone on Toes, Tre and Tsl is documented in Table 4.4. Naloxone did not significantly alter any of the temperature measurements at rest. The Toes response to maximal graded exercise testing was not significantly different from placebo and naloxone. The highest Toes, Tre and Tsl recorded during maximal graded exercise testing were not significantly modified by naloxone.

The magnitude of the rise in Toes from resting levels in response to maximal graded exercise testing was greater ($p<0,001$) than that for Tre and Tsl, with and without endogenous opioid antagonism. The rise in Toes (placebo: $2,2 \pm 0,4^{\circ}C$ rise, $p < 0,001$) and Tre (placebo: $1,1 \pm 0,2^{\circ}C$ rise, $p < 0,001$; naloxone: $0,9 \pm 0,4^{\circ}C$ rise, $p < 0,001$) was significant with placebo and naloxone. In contrast, the rise in Tsl (placebo: $0,5 \pm 0,5^{\circ}C$ rise, $p < 0,05$; naloxone: $0 \pm 0,8^{\circ}C$ rise, $p > 0,5$) was significant only with placebo. However as a result of considerable interindividual variation, the magnitude of the rise in Tsl was not significantly different ($p>0,1$) with placebo and naloxone. In agreement with previous research (Grossman et al , 1984 ; Willer et al , 1978 ; Staessen et al , 1985) naloxone did not significantly alter any of the investigated cardiorespiratory parameters (Table 4.5). Likewise, the maximal exercise duration during graded cycle ergometer testing was similar with placebo and naloxone (Table 4.5).

TABLE 4.4

THE EFFECT OF 2 MG NALOXONE ON THE OESOPHAGEAL (Toes), RECTAL (Tre) AND SUBLINGUAL (Tsi) TEMPERATURES DURING MAXIMAL EXERCISE (PART II)

	TES (^{0}C)		TRE (^{0}C)		TSI (^{0}C)	
	PLACEBO	NALOXONE	PLACEBO	NALOXONE	PLACEBO	NALOXONE
Rest	36.8±0.3	36.9±0.3	37.2±0.3	37.2±0.3	36.4±0.5	36.7±0.8
80W	36.7±0.3*	36.7±0.4*				
120W	37.0±0.3*	37.0±0.5				
160W	37.4±0.3*	37.3±0.4*				
200W	37.8±0.3*	37.7±0.5*				
240W	38.0±0.4*	37.9±0.5*				
Peak	39.0±0.4*	39.0±0.4*	38.3±0.4*	38.1±0.4*	36.9±0.6*	36.7±0.5

Values are mean ± SD; n = 8. Peak = highest temperature recorded.
Temperatures did not differ significantly with placebo and naloxone.
* $p<0.05$ versus resting value.

TABLE 4.5

THE EFFECT OF 2 MG NALOXONE ON THE CARDIORESPIRATORY RESPONSE TO MA EXERCISE (PART II)

	PLACEBO	2MG NALOXONE
Resp rate (breaths/min)	57 ± 13	58 ± 12
$\dot{V}_E$ (1/min)	152.4 ± 22.6	152.7 ± 20.4
$\dot{V}O_2$ max (1/min)	4.37 ± 0.61	4.32 ± 0.60
$\dot{V}O_2$ max (ml/kg/min)	62.8 ± 6.5	61.8 ± 7.2
$\dot{V}CO_2$ (1/min)	4.83 ± 0.66	4.80 ± 0.62
RER	1.11 ± 0.06	1.12 ± 0.06
HRmax (beats/min)	181 ± 7	184 ± 6
Time (min)	20.45 ± 2.77	20.33 ± 2.09

Values are mean ± SD; n = 8. Resp rate = respiratory rate at m exercise; $\dot{V}_E$ = pulmonary ventilation at maximal exercise; $\dot{V}O_2$ maximal O_2 uptake; $\dot{V}CO_2$ = CO_2 output atmaximal exercise; R respiratory exchange ratio at maximal exercise; HRmax = maximal rate; Time = exercise test duration. Placebo and naloxone did not significantly.

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CHAPTER FIVE

DISCUSSION

5.1 NALOXONE ADMINISTRATION AND THE THERMOREGULATORY RESPONSE TO EXERCISE

5.2 NALOXONE ADMINISTRATION AND THE CARDIOVASCULAR RESPONSE TO EXERCISE

5.3 NALOXONE AND THE VENTILATORY RESPONSE TO EXERCISE

In these two studies a number of important observations are made regarding the effect of naloxone administration on the:

- themoregulatory response to exercise
- cardiovascular response to exercise
- ventilatory response to exercise

5.1. NALOXONE ADMINISTRATION AND THE THERMOREGULATORY RESPONSE TO EXERCISE

In Part I of the study it was shown that neither 2 mg nor 10 mg naloxone alters the rectal temperature response to 30 min submaximal exercise. Furthermore the calculated water loss during the exercise period was not altered by naloxone administration. It may be argued that in this study, either the degree of opioid receptor blockade was not sufficient or the endorphin rise in response to the submaximal exercise was not sufficiently great to demonstrate any physiologic effect.

The degree of receptor blockade would only be insufficient if the naloxone concentration in the blood was not high enough to facilitate receptor blockade during the exercise period, or if the naloxone that was administered was inactive.

The latter possibility is extremely unlikely as two different batches of naloxone were used in the two parts of the study.However no verification of activity could be done as the supply from each batch was just sufficient to complete the experiments.

Unless the phamacokinetics of naloxone changes as a result of exercise, the physiologically high dose (10 mg) of naloxone would result in adequate blockade particularly if only 0,4 mg is normally needed to reverse the effects of morphine administration in humans . Furthermore, the reported serum half life of naloxone is ~ 60 min (Ngai et al , 1976) and this far exceeds the 45 min period from the time of naloxone injection to the end of exercise in this study. Therefore the argument that the degree of opioid receptor blockade by naloxone was not sufficient does not hold with respect to this study.

The rise in plasma B-endorphin levels during exercise depends on a number of factors including exercise intensity and duration (Section 3.5.1). In this study it could be argued that the relative intensity (~ 55 % at $\dot{V}O_2$ max) as well as the duration (30 min) may not have been adequate to stimulate endorphin release. However, in Part II of the study, 2 mg naloxone failed to alter the rectal and oesophageal temperature responses during a maximal exercise test. This indicates that naloxone blockade of endogenous opioids during either low intensity submaximal or short duration maximal exercise fails to alter the core temperature responses.

Although the rectal and oesophageal temperature responses were not affected by naloxone administration, Part II of the study

showed that sublingual temperature did not rise after naloxone administration. The use of sublingual temperature as an indicator of core temperature is questionable, particularly during or immediately following exercise as high ventilatory rates make measurement difficult (Mairiaux et al , 1983). The precise reason for the failure of sublingual temperature to rise during exercise following naloxone infusion is not clear. In some way the local heat exhange mechanisms in the oral cavity must be altered by naloxone so that heat loss is increased. A possible mechanism could be an alteration in local blood flow induced by naloxone particularly as B-endorphin has been demonstrated to affect blood flow in the cheek pouch of the hamster (Wong et al , 1981). This however would require further investigation.

The following conclusions can be drawn from these studies with respect to naloxone administration and the thermoregulatory resonse to exercise:

- Naloxone administration does not alter the core temperature response to submaximal and maximal exercise.

- The failure of naloxone to alter core temperature responses during exercise is not dose dependent.

- Naloxone selectively appears to alter heat exchange mechanisms in the oral cavity possibly by altering local blood flow.

- Naloxone administration does not alter the rate of water loss during submaximal exercise.

- There is general agreement, based on sufficient evidence, that endogenous opioids alter core temperature in the resting animal. However in this study it is concluded that insofar as naloxone may be used as tool to investigate the endogenous opioid system,

endogenous opioids do not play a role in temperature regulation during exercise.

5.2. NALOXONE ADMINISTRATION AND THE CARDIOVASCULAR RESPONSE TO EXERCISE

In Part I of the study neither 2 mg nor 10 mg naloxone administered intravenously altered the heart rate response, systolic blood pressure response or the diastolic blood pressure response to submaximal exercise. Furthermore Part II of the study showed that neither peak heart rate nor exercise duration was significantly altered by 2 mg naloxone administration. These findings are in keeping with those in other studies (Grossman et al , 1984 ; Willer et al , 1979 ; Staessen et al , 1985).

It could therefore be concluded that naloxone antagonism of the endogenous opioid system does not alter the cardiovascular response to exercise irrespective of the naloxone dose used or the exercise intensity.

5.3. NALOXONE ADMINISTRATION AND THE VENTILATORY RESPONSE TO EXERCISE

Although it has been demonstrated that naloxone can increase peak ventilation during exercise (Grossman et al , 1984), this was not confirmed in either Part I or Part II of this study. In Part I and Part II of the study naloxone did not alter ventilation, oxygen consumption or carbon dioxide production during steady state submaximal (Table 4.2) and maximal exercise (Table 4.5) respectively.

In this study it is concluded that naloxone administration does not alter the ventilatory response to exercise irrespective of the dose of naloxone used or the exercise intensity.

CHAPTER SIX

SUMMARY

A study was conducted in two parts to examine the effect of naloxone administration on thermoregulatory responses during exercise. In particular the following variables were studied: Naloxone dose, exercise intensity, exercise duration and site of core temperature measurement. The results of the studies show that naloxone does not influence core temperature responses to either maximal or prolonged submaximal exercise. The dose of naloxone used did not influence the thermoregulatory response to exercise. The oesophagus and rectum are reliable sites for core temperature measurement. However, as naloxone administration selectively abolishes the rise in sublingual temperature during exercise this site appears to be an unreliable indicator of core temperature in studies such as these. The reasons for the failure of the sublingual temperature to rise following naloxone administration are not clear and require further investigation. Thus, insofar as naloxone may be used to investigate the endogenous opioid system, it is concluded that endogenous opioids do not play a significant role in temperature control during exercise.

APPENDIX A

PROPOSED CRITERIA NECESSARY TO IMPLICATE THE ENDOGENOUS OPIOID SYSTEM IN A PHYSIOLOGIC PROCESS :

- Antagonism of a physiological or a pharmacological response by naloxone hydrochloride.
- Demonstration of cross tolerance with morphine.
- Demonstration that other opioid antagonists produce the same effect as naloxone.
- Demonstration that antagonists which lack opiate antagonist activity are inactive.
- Demonstration that agents which inhibit the breakdown of endogenous opioid peptides potentiate the naloxone antagonized response.
- Demonstration of a direct release of opioid peptides by the stimulus.

Adapted from Sawynok et al (1979)

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