CHAPTER II

LITERATURE REVIEW

Opium is one of the oldest medication known in history of medicine. It has long been used as an analgesic since ancient Chinese and Egyptian records dating before 200 B.C.(Bovill,1987). In Thailand, opium dependence was reported as far back as 600 years ago by the Three Signate Code in 1978 (Poshyachinda,1982). Interestingly, the data in 1959-1960 from the Opium Treatment Center in Rangsit indicated that the age of chronic opiate users ranged between 21-30 years old, however, indicating some shift to asomewhat younger age-group(Poshyachinda,1982).

Morphine, a derivative of opiate alkaloid is the commonest agent used in clinical medicine. It is a basic amine, rapidly metabolized and excreted from the body and produced plasma levels of free morphine from 15 minutes to 3 hours with a peak plasma levels occurring within 20 minutes after intramuscular or subcutaneous injection (Brunk and Delle, 1974, Stanski et al., 1978). It is well absorbed from the gastrointestinal tract and rapidly conjugated with glucuronide in the cells of the intestinal mucosa and liver. Therefore, N-demethylation of morphine is greater after oral intake than after intravenous administration (Brunk and Delle, 1974, Rane et al., 1984). However, plasma half-life of morphine in human subject varied between 114 - 132 min., irrespective of range (Spectorand Vesell,1971, Brunk and Delle, 1974, Stanski el al., 1978, Sawe et al.,1981), the rhesus monkey, however, showed 102- 202 min. (Rane et al .,1984).

Evidence during the past decades had showed the existence of several endogenous opiate peptides in several tissues. These peptides are capable of interacting with the identical receptor of the opiate alkaloids(Quigley and Yen,1980, Howlett and Rees,1986). Studies the specific binding sites in brain and other organs suggested the existence of different opiate receptors including mu(μ),kappa(k),delta(δ) and sigma(σ) receptors (Mansour et al.,1988). Although there is considerable variation in binding characteristics and chemical distribution of receptors among different species, inferences have been drawn that same receptor such as morphine and β-endorphin, are potent agonist at mu receptor, have been associated with analgesia. This receptor is considerably more sensitive to naloxone antagonism than the sigma and kappa types (Lightman and Everitt,1986, Snyder,1984).

The Opiate and Reprouduction

Evidence in animal models and chronic addict cases indicate that morphine and related opiates exert affect on normal physiology and behaviour (Guerra,1974, Mirin and Myer, 1978, Mirin et al.,1980). In animal studies, acute treatment with morphine and its synthetic analogue, methadone, induce suppressive effects onmounting, intromissional and ejaculative behaviours of the male rats and hamsters(Hetta,1977, Murphy,1981). Sawyer et al.(1955), Barroclough and Sawyer (1955) were among the pioneer scientists in this area who demonstrated that acute treatment with a single dose of morphine and other central neural depressants, in female rats, prior to the "critical peroid" for the neurogenic stimulation of ovulation in.

the afternoon of proestrus were capable of postponing ovulation time for 24 hours. Male patients with heroin or morphine addiction often complain of frigidity, loss of libido and impotence. Associated symptoms include difficulty in achieving orgasm, decreased frequency of sexual intercourse and ejaculation (Gaulden et al.,1964, Cushman,1972, DeLeon and Wexler,1973, Hellman et al.,1975, Renshaw,1978, Crowley and Simpson, 1978, Cicero et al.,1979, Mirin et al.,1980, Blankstein et al.,1981).In morphine addicted women, ovarian dysfunction, anovulation, amenorrhea with sterility are common (Gaulden et al., 1964, Stoff,1968, Mintz et al.,1974, Santen et al., 1975). Chronic addiction during pregnancy frequently associates with spontaneous abortion (Wallach,Jerez and Blinick,1969). In the event that foetus survive until term, the infant has a higher of perinatal morbidity and mortality with relatively lower birth weights and smaller size for gestational age, due to prematurity and intrauterine growth retardation (Reddt, Harper and Stern,1971, Zelson, Rubio and Wasserman,1971, Friker and Segal,1978).

- Effects of opiate on the hypothalamic-pituitary-gonadal axis

Acute administration of morphine and related opiates consistently induces suppression of basal serum levels of LH and FSH in both male and female rodents (Cicero et al.1976, Bruni et al.,1977, Pang et al.,1977, Meites et al.,1979, Kalra and Gallo,1983). Significant decrease frequency and amplitude of pulsatile LH secretion have also been reported in female and male rhesus monkeys after acute intravenous injection of morphine (Spies et al.,1980, Ferin et al., 1982, Gilbeauet al., 1983,

Abbott et al., 1984, Orstead, Hess and Spies, 1987). Furthermore, Gilbeau et al. (1985) found acute suppression of basal LH levels in adult male rhesus monkeys within 1 hour of injection. Acute of administration enkaphalin analogue in normal men and women induce sudden decrease in circulating LH levels (Von Graffenried et al.,1978, Stubbs et al., 1978, Del Pozo et al., 1980, Grossman et al.,1981). Similar effects were also reported in detoxified male addicts acutely injected with heroin (Mirin et al., 1980).

If opiate is given into female during late follicular phase of the cycle, preovulatory rise of serum FSH and LH are always suppressed in rats (Ieir et al.,1980, Ching,1983, Kalra and Gallo,1983, Blank et al.1986) rhesus monkeys (Abbott et al.,1984) and humans (Stubbes et al.,1978, Grossman et al., 1981). Moreover, lower pulsatile levels of LH also found in chronic addicted men (Wang, Chan and Yeung,1978, Brambilla et al., 1979) and women (Mirin et al.,1980, Blankstein,1981, Delitala, Grossman and Besser,1983).

The disruptive effects of these opiates on reproduction and their inhibitory effect on gonadotrophin levels, led some investigators to postulate that the opiates might play a role in physiological control of reproductive hormones (Meites et al., 1979, Grossman et al.,1981, Ropert, Quigley and Yen,1981). Several studies in laboratory rodents indicated that the opiates do not modulate gonadotrophin secretion from the adenohypophysis but rather act on the hypothalamus by interfering with pulsatile GnRH secretion (Cicero et al.,1977, 1980, Simantov and Synder,1977, Pang, Zimmerman and Sawyer,1977, Stubbs et al.,1978, Delitala et al.,1980, Lightman et al.,1981, Ferin etal.,1982,

Kalra and Leadem,1984, Thind and Goldsmith et al.,1988). The mechnism of the opiates modulated release of GnRH appears to involve an interaction with hypothalamic monoamines including dopaminergic and serotoninergic systems (Van Loon and De Souza,1978, Fuxe et al.,1980). More recent works suggested the possibility of opiate/adrenergic interaction regulation of LH secretion (Kalar and Kalra,1984, Lightman and Everitt,1986). Nevertheless, the results of *in vitro* study suggested that long term exposure of rat adenohypophyseal cells to exogenous opiates may acts directly upon specific opiate receptors in gonadotrophs leading to suppression of FSH and LH secretion (Barkan et al., 1983, Blank et al.,1986, Chao, Moss and Malven,1986). Direct action of opiates on the hypothalamic-pituitary axis as stated would eventually affect on gonadal steroids secretion and sex accessory gland function (Nappi et al.,1987, Quigley et al.,1980, Blankstein et al.,1981, Petraglia et al.,1987, Smith and Asch,1987).

- Relationship of sexual behaviour and reproductive hormones

In male non-primates, sexual behaviour is clearly hormone-dependent, the frequency and level of sexual performance are correlated with the concentration of plasma testosterone, as it declines after castration followed by a decrease in copulatory behaviour and penile reflex. The decline is reversed by replacement therapy with testosterone (Beach,1945, Resko and Phoenix, 1972, Clark et al., 1988). The decline in sexual behaviour after castration is often slow, taking several weeks to reach its maximal although plasma testosterone levels is undetectable within hours. Similary, replacement therapy with testosterone after long-term castration will also take several

weeks to reverse the castration changes and resumption of sexual behaviour. This suggested that an insensitivity to the hormone develops progressively in the target tissues that mediates these behaviours.

In male monkeys, castration may eventually be followed by a reduction in sexual activity. Greatly reduced in the number of mount, intromission and ejaculation in rhesus monkey is found after several weeks of castration, but often the reduction does not proceed to total loss. Whereas the systemic testosterone levels is significanlty lowerwithina fewhours after testicular removal (Resko and Phoenix, 1972, Michael and Wilson,1974). The testosterone replacement therapy is effective in then restortion of sexual behaviours, the time course ranges is found between 14-17 weeks, but only partial on ejeculation. However the extent and time course dependent on several other factors such as age, sexual experiences and individual difference in performance (Michael and Wilson,1974).

In female non-primates sexual behaviour is more hormone-dependent than in males (Ciaccio and Lisk,1971 Baranczuk and Greewald,1973, Caster et al,1976, Clark et al.,1988). Receptivity occurs cyclically and is closely linked with the period of ovulation which ensures that copulation occurs at a time when successful fertilization is possible (Beyer and McDonald,1973, Carter et al.,1976, Huch, Carter, Banks,1979). Ovariectomy is followed by a prompt and usually complete abolition of receptivity and proceptivity. Restoration of these elements of female's sexual behaviour is achieved equally rapidly by immediate treatment with estradiol-17β but inhibited by progesterone (Beyer and Mcdonald,1973, Dluzen and Carter,1979).

The strict relationship between ovarian hormones and sexual behaviour in non-primate mammals is largely lost or altered in primates. In female non-human primates, sexual interaction between a male and female monkey is often seen to follow a cyclic pattern of the menstrual cycle (Zumpe and Michael,1970, Michael et al.,1972, Rowell,1972,Slob et al.,1975, Mendoza et al.,1978, Michael and Zumpe,1988). Receptivity in female and attractiveness of the male are dependent upon the presence of estrogen in female during mid-cycle. These activities decline during luteal phase of the cycle (Michael and Harris,1964, Hisaw and Hisaw,1966, Zumpe and Michael,1970). Cyclic variations in sexual behaviours are abolished by ovariectomy and sexual activities can be restored by estrogen administration. Thus providing strong evidence that behavioural change depend on the secretory activity of ovarian steroids (Michael, Herbert and Welegalla,1967, Michael, Saayman and Zumpe,1968, Michael and Welegalla,1968, Michael and Zumpe,1984).

Numerous experiments have pointed quite consistently to the vagina as the site where estradiol and progesterone extert these effects known as pheromone. Oestradiol surge at the mid-cycle causes LH rise and sexual attraction (Zumpe and Michael, 1983,1985) and acts principally on peripheral mechanisms in vagina to increase attractive activity(Michael and Saayman,1968, Johnson and Phoenix,1976). Apparently, estrogen stimulated vaginal secretion is a good substrate for local microorganism to utilize and alter the secretion to volatile substances composing of a mixture of simple aliphatic acid that function as stimulating "pheromone" (Michael and Keverne,1970, Keverne,1976). Presumably signals from the vaginal secretion affect via

olfactory of the male partner and play an important role in male and female sexual interaction. Conversely, progesterone, the luteal phase hormone, decrease the sexual attractiveness of female monkeys and this probably the major cause of decreasing in sexual interactions (Keverne and Michael,1971, Michael and Zumpe,1982).

These evidences indicate that the gonadal steroid probably act directly on specific neuronal cell in central nervous system to modulate these sexual behaviours (Trimble and Herbert, 1986, Dixson and Herbert, 1974, Everitt and Herbert,1971,1975). It has been a consistent finding that lesions placed in the medial preoptic area and adjacent anterior hypothalamus of non-primates abolish sexual behaviour. Conversely, implantation of testosterone into the preoptic-anterior hypothalamic area, which are rich in androgen receptor, restores sexual behaviour in castrated male rats (Clark et al., 1988, Johnson and Everitt,1988). Similarly, lesion in thepreoptic area of male rhesus monkey greatly lessened copulation frequency with its partner (Johnson and Everitt,1988).

A similar hypothalamic site of action of oestradiol also existed, butthe ventromedial nucleus(VMN) rather than the more anterior preoptic areas seems to be the principal site of action of the hormone in female rodent. Thus oestradiol implanted in the VMN in amounts sufficient to saturate of the oestrogen receptors there increase markedly the receptive behaviour of ovariectomized female rats. Further *in vitro* study confirmed that 24 hours after exposure with E_2 initiates specific morphological and chemical changes of neurons. Typical changes include increase in synaptic density RNA and protein synthesis

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(Parsons et al.,1981,1982, Jones, Pfaff and McEwen,1985, McEwen, Jones and Pfaff,1987)..

In female monkeys, androgens which notably testosterone rather than oestrogen seem to underlie in sexual behaviour. Their behavioural effects are also apparently mediated in the vicinity of VMN and preoptic area (Dixson and Herbert,1974, Everitt and Herbert,1975). Testosterone is capable of stimulating proceptivity and sexual invitation in ovriectomized rhesus monkeys. It is has been suggested that testosterone is aromatized to oestrogen in the brain (Ryan et al.,1972). However, Johnson and Phoenix (1976) suggested that the female sexual behaviour is regulated by suitable ratio of both oestrogen and androgen.

The Opiate and Regulation and Prolactin Secretion

Prolactin release is controlled by prolactin inhibiting factor(PIF) and hypothalamic prolactin releasing factor(PRF). The most important PIF identified is dopamine which is found in neurons of the arcuate nucleus whose axons project to the portal capillaries in the medial and lateral palisade zones of the median eminence. Dopamine is secreted into the portal blood from the tubero-infundibular dopamine (TIDA) system and transported to the lactotroph (Brown, Seeman and Lee,1976). In addition, norepinephrine secreted from neurons of the arcuate nucleus is also capable of inhibiting prolactin (PRL) secretion *in vivo* (MacLeod,1969) and *in vitro* (Birgeetal.,1970). Other candidate for PIF secreted from the hypothalamus included, gamma-aminobutyric acid(GABA) (Schally et al.,1977, Clement, Shaar and Smalstig,1980) and the GnRH-associated peptide(GAP)(Johnson and

Everitt,1988). It is of interest that GABA neurons from the arcuate nucleus also project their axon terminal to the portal capillaries of the median eminence. Recently, GAP, a fragment of GnRH prohormone molecule, has been shown to inhibit PRL secretion being able to promote gonadotrophin secretion (Johnson and Everitt,1988)..

A variety of hormones has been shown to stimulate PRL secretion. A tri-peptide of hypothalamic thyrotrophin releasing hormone (TRH) was the first hypothalamic factor capable of stimulating PRL release (Spieset al.,1980). *In vitro* study also showed TRH direct stimulating effect on PRL secretion from the pituitary (Tashjian, Barowshy and Jensen,1971). It is of interest that the vasoactive intestinal peptide (VIP) has a potent stimulating effect on PRL secretion (Johnson and Everitt,1988, Lam 1989). Whether, this active agent has direct stimulating effect on the adenohypophysis or indirect via inhibition of TIDA activity and stimulation of opiate receptor has not been conclusively determined (Kato et al.,1978) although specific VIP receptors are identified in lactotroph and peak secretory activity of VIP has been detected during active lactation (Johnson and Everitt,1988). VIP containing neurons have been identified in the parvocellular paraventicular nucleus and a rich terminal plexus becomes visible in the external layer of the median eminence (Kiss etal.,1985). Lastly, estrogens can also exert stimulating effect on PRL secretion, probably by decreasing the sensitivity of lactotroph to dopamine and by increasing the number of TRH receptors (Quadri, Norman and Spies,1977, Spies et al.,1980). However, to estrogen induced release of PRL is not as rapid as other agents mentioned and may

not fulfill the property of PRF (Johnson and Everitt,1988).

By contrast with circulating gonadotrophin levels, acute and chronic administration of opiates are capable of stimulating increment of PRL secretion in rodents (Meites, Nicoll and Talwalker,1959, Lal,1975, Bruni et al.,1977, Spiegel, Kourides and Pasternak,1982, Almeida, Schulz and Herz,1986), monkeys (Gold, Redmond and Donabedian,1979, Spies etal.,1980, Gosselin et al.,1983,1985) as well as humans (Tolis, Hickey and Guyda,1975, Von Graffenreid et al.,1978, Demura et al.,1981, Grossman, 1981, Reid, Quigley and Yen,1983, Delitala, Grossman and Besser,1983). Overwhelming evidences indicated direct action of opiates on their specific receptors within arcuate nucleus to suppress dopamine secretion from TIDA neurons, thereby enhancing pituitary gland secretion of PRL (Van Vugt et al.,1979, Wardlaw et al.,1980, Haskins et al.,1981, Lookingland and Moore,1985, Dawood, Khan-Dawood and Ramos,1986, Grossman,1987). Gudelsky and Porter(1979) further found in rats that subcutaneous injection of morphine or intraventricular administration of endorphin produced 85-95% reduction in dopamine concentration in pituitary stalk plasma. Since opiate receptors in the TIDA neurons projecting into the median eminence overlap extensively with several other hypothalamic neuron terminals, including the neurons containing GABA, serotonin, norepinephrine and GnRH neuron terminals (McNeil and Sladek,1978, Watson et al.,1978, Grossman,1981). It has been suggested that dopamine may also exert as an inhibitory neuromodulator of GnRH release (Fuxe et al.,1973, Petraglia et al.,1988). Clinically hyperprolactinemic women always have high levels of endogenous opiates in then systemic circulation and are usually associated with amenorrhea

(Petraglia et al.,1987). However, *in vivo* and *in vitro* studies indicated that the regulation of LH and PRL secretion are very complex and may mediated by different type of opiate receptors (Spiegel et al.,1982, Koening, et al.,1984, Wiesner et al.,1985, Pfeiffer,1987). On the other hand, Shin et al.(1988) found that morphine was able to stimulate PRL release with absence of functional dopaminergic PIF receptors and concluded that stimulating effect of morphine on PRL release may be independent of dopaminergic mechanism. Amoroso et al. (1988) further suggested that this complex mechanism may involve several opiate receptors and the opiates may exert their PRL releasing effect via mediation of other brain biogenic compounds including catecholamines (Anden et al., 1970, Gold et al., 1978), histamine (Arekelian and Libertum,1977), angiotensinII (Aguilera, Hyde and Catt,1982) and serotonin (Kamberi, Michael and Poster,1971, Spampinato et al.,1979, Bero and Kuhn,1987) which provide the functional link between CNS and neurosecretory neurons for PRL control (McCann and Moss,1975). Additionally, some evidences demonstrated that opiates can also directly sensitize the adenohypophyseal lactotroph to TRH independent of its major role on inhibition of the dopaminergic tone (Snowden, Khan-Dawood and Dawood,1984, Buydens et al.,1987).

The Opiate and Adrenocortical Activity

Several lines of evidences in laboratory rodents indicated that acute administration of opiates may also stimulate corticotrophin releasing factor (CRF) secretion from the hypothalamus followed by the release of ACTH and finally cortisol from adenohypophysis and adrenal cortex(Meites et

al.1979, Van Vugt and Meites,1980, Beyer et al.,1986, Bailey and Kitchen,1987, Estiene et al.,1988). The stimulation of hypothalamic-pituitary-adrenocortical activity by opiates is presumably due to stimulation of specific CRF neuron receptor in hypothalamus (Buckingham and Hodges, 1979, Buckingham, 1982). However, prolong administration of the opiate agonist to rats may lead to suppression of the pituitary-adrenal axis (De Souza and Van Loon,1982, Grossman and Rees,1983). *In vitro* studies in rats further suggested that long term action of the opiates may directly suppress pituitary ACTH response to CRF (Lamberts et al.1983). Moreover, opiates may also exert a direct effect on adrenocortical cells and decrease their sensitivity with ACTH (Beyer et al.,1986). Unlike the rat, serum ACTH and cortisol levels apparently inhibited by acute intravenous administration of enkephalin analogue in chimpanzee (Gosselin et al.,1983) and in humans injected intravenously with morphine (Tolis, Hickey and Guyda,1975, Blankstein et al.,1980, Taylor, Dluhy and Williams, 1983, Beyer et al.,1986, Grossman,1988). Subjects suffered from chronic heroin addiction also showed reduction of ACTH and cortisol secretion (Hellman et al.,1975, Ho et al.,1977). On the other hand, recent report by Almeida, Nikolarakis and Hrez(1988) that CRF may capable of stimulating the release of endogenous opiates which in turn inhibits GnRH neuron activity and gonadotrophin secretion.

Environmental Stress, Opiate and Fertility Regulation

It is generally accepted that changes of the hypothalamic-pituitary-adrenal activity would affect normal behaviour of animals and human. Selye (1936) described

morphological changes and found hypertrophy of the adrenal glands but the atrophic thymus in rats chronically exposed to various stressful conditions. The latter was associated with suppression of immune mechanism. Further studies in rodents suggested that a variety of physiological conditions including experimental trauma and novelty stress result in elevated levels of both cortisol and PRL (Seggie and Brown,1975, Johnson and Negro-Vilar,1986, Muir and Pfister,1986). Primarily exposure to social stress leads to an immediate rise in serum ACTH and cortisol that and will last as long as the stressor is present (Manogue, Leshner and Candland,1975, Hennessy,1986). On the other hand, chronically stressed rats showed a lower serum cortisol concectration than their pre-stress levels, while serum levels of ACTH were not altered (Sakellaris and Vernikos-Danellis,1975, Burchfield,1980, Armario and Castellanos,1984). In both primates and humans plasma levels of 17β-hydroxy corticosteroid and PRL also raised after acute stressful conditions (Mendoza et al.,1979, Puri, Puri and Anand Kumar,1981, Florica et al., 1982, Adrian et al.,1988). On the other hand, prolong exposure to these stresses lead to a decline in serum adrenal cortisol levels (Coe et al.,1978, Hennessy,1986).

Increase serum levels of cortisol and enlargement of adrenal gland are frequently found among lower ranking monkeys than in higher ranking monkeys (Sassenrath,1970, Browman, Dilley and Keverne,1978, Keverne,1979, Eberhart, Keverne and Meller,1983, Shively and Kaplan,1984). The hormone feedback and modification the subsequent behavioural response of individual to those stressful stimuli may be likened to showing conditional emotional responses in order to survive in particular social

situation and the mechanisms of the emotion on the hormonal changes may mediate via higher center through the hypothalamic-pituitary axis (Levine,1970, Leshners and Candland,1972, Aguilera,1986).

However, morphine reduced the stress-induced increased in plasma levelsof ACTH corticosterone as well as PRL in rodents (John and Negro-Vilar, 1986, Suemaru et al.,1989) and monkeys (Glowa and Barrett,1983, Brady and Barrett,1986). In this regard, at least part of opiates- and stress- induced increase in PRL apparently result from a decrease in dopamine inhibitory tone in the median eminance. Evidences in rats suggested that stress activates a neuronal opiate pathway by stimulation of serotoninergic activity in the medial basal hypothalamus. This serotoninergic activation may either directly or indirectly inhibit dopaminergic neurons transmission in the median eminance (Ragavan and Frantz, 1981, John and Negro-Vilar, 1986), although more recent evidences have regarded PRL as an important immunoregulatory hormone as well (Healy et al.,1990).

The role of the adrenal cortex in mating behaviour and circulating testosterone levels is well documented in male rodents (Nequin and Schwartz,1971, Barfield and Lisk, 1974, Plas-Roser and Aron,1977). It is also well known that the stressful manipulations such as immobilization, surgery and/or anaesthesia contribute to progesterone secretion into the peripheral blood as plasma cortisol levels which are associated with delayed puberty in young mice (Pairs and Ramaley,1974) and changes in the levels of oestrous sexual receptivity in adult female rodents (Feder, Resko and Guy,1968, Barfield and Lisk,1970, Plas-

Roser, Paris and Ramaley,1974).

Studies of primate living in social groups have revealed that the social context in which individuals interact can change their endocrine status. In groups of these monkeys, consisting of males and females, only the dominant male showed high incidence of socio-sexual interactions. He directs his aggression to subordinate males but does not receive any aggression from them. Measurement of plasma testosterone shows significant rise in the dominant male but not in the subordinates (Eberhart, Keverne and Meller,1983). A similar dominance hierarchy is also seen in females. The dominant female receives more attention from the male than does the subordinate female, and hardly ever receive any aggressive behaviour from other female members. Subordination in these male and female monkeys seem to be associated with stress induced infertility. Most of these monkeys secrete more cortisol and PRL than the dominant monkeys (Bowman, Dilley and Keverne,1978, Keverne,1979, Eberhart, Keverne and Meller,1983). That high PRL levels are associated with amenorrhea and failure to ovulate. However, subordinate female marmosets isolated from the group and paired with a male may resume their normal cyclicities follow by successful pregnancies(Epple,1978, Abbott and Hearn,1978).

The role of CRF in the stress-mediated decrease LH secretion has been investigated *in vivo* and *in vitro*. The result showed that CRF exerts a central nonadrenal-mediated inhibitory influence on pulsatile LH and FSH release by reduction of GnRH secretion mediated by via endogenous opiates (Blank et al.,1986, Gindoff and Ferin, 1987, Petraglia et al., 1987). In turn, some of endocrine abnormalities induced by

stress may be related in part to increase CRF accompanying with rise in opiate tones (Plotsky and Vale, 1984, Petraglia, Vale and Rivier, 1986, Almeida, Nikolarakis and Herz,1988).

The Opiate and Other Pituitary Hormones

Morphine and related opiates decrease the sensitivity of hypothalamus to affect stimulation on the adenohypophysis. This would lead to decrease in pituitary trophic hormone concentrations (Briggs and Munson 1955, Buckingham,1982). The opiate may affect hypothalamic TRH neurons needed for regulation of pitutary TSH secretion. In some species, TSH secretion is inhibited but this effect does not appear to be prominent or consistent in human subjects (Tolis, Hickey and Guyda,1975, Bruni et al.,1977, Grossman et al.,1981, Jaffe and Martin,1985, Jordan et al.,1986). *In vitro* study using superfused medial basal hypothalamic slices have demonstrated that both leu-enkephalin and morphine significantly inhibit the K^+ depolarization - induced releas of TRH (Tapia-Arancibia and Astier,1983). On the other hand, endogenous opiate peptides may have direct stimulating effect on the release of TSH from the adenohypophysis (Judd and Hedge,1983).

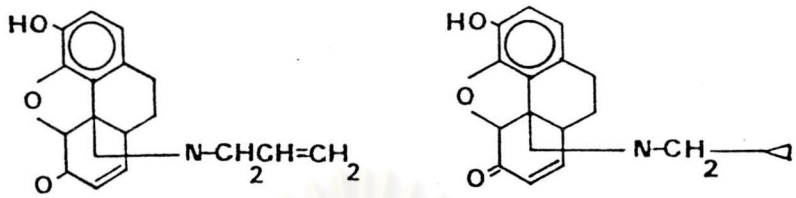
Opiate alkaloids and opiate peptides have been shown to stimulate the release of growth hormone and this effect appears to be primarily mediated by growth hormone releasing hormone,GRH, (Miki et al.,1984) and inhibition of hypothalamic somatostatin (Drouva et al.,1981, Spiegel, Kourides and Pasternak,1982). Under physiological conditions a number of hypothalamic neurotransmitter systems may be associated with the opiate peptides in regulation of plasma growth hormone levels. These

include GABAnergic, dopaminergic and cholinergic path ways (Grossman and Rees,1983). However, the exact mechanism how opiate peptide controls growth hormone release is still largely not understood. (Lightman and Everitt, 1986).

The opiate peptide and opiate receptors are present in the magnocellular areas of the paraventricular and supraoptic nuclei of the hypothalamus. However, only opiate receptors are present in the posterior pituitary(Mansour et al.,1988). Thus the opiates may directly play a role in regulation of neurohypophyseal hormone secretion. Halder and Sawyer(1978) showed that morphine inhibited suclking induced oxytocin release in mice, but the other works found morphine stimulate the release of antidiuretic hormone (Weitzman et al.,1977, Bisset, Chowdrey and Feldberg, 1978).

Mechanism of Morphine Actions.

Recently, specific opiate antagonists are synthesized and used as tools for identifying opiate receptors and for detoxification proceduce for drug addicted patients. Among these worthy agents naloxone and naltrexone (figure 3) are morphine derivatives having relatively high affinity for opiate binding sites of mu receptor. Their affinity for kappa receptor is about one-twentieth that for mu receptor and probably even less for delta receptor(Bruni et al., 1977, Morlry et al.,1980, Pontiroli et al.,1982, Van Vugtetal., 1983, Abbott et al.,1984, Way and Way,1987, Agmo and Paredes, 1988, Steiman et al., 1990).



naloxone naltrexone

Figure 3. Structures of opiate antagonists

It has been reported that administration of naloxone to normal human male subjects stimulate penile erection and erotic thoughts (Mendelson et al.,1979). Similarly, the drug also increases the mating frequency and decreased the number of intromission or mounts which required to achieve ejaculation in male rats (Meyer and Baum,1979, and McIntosh et al.,1980). However, Abbott et al. (1984) found little change in sexual behaviours of rhesus monkeys following opiate antagonist treatment except slightly increase in proportion of female approaches to male.

Naloxone increases frequency and amplitude of LH pulse (Quigley et al.,1980, Ropert, Quigley and Yen,1981, Ellinboe et al.,1982) and the effect is most marked in late follicular and mid-luteal phases (Quigley and Yen,1980, Van Vugt, Lan and Ferin,1984, Snowden, Khan-Dawood and Dawood,1984,1986), whereas changing in circulating levels of FSH is not pronounced. Abbott et al. (1984) suggested that the gonadotrophic stimulating of

the opiate antagonist was specific to LH. In postmenopausal or ovariectomized women naloxone is unable to further elevate LH, but the sensitivity is restored by replacement with oestradiol-17β and/or progesterone (Denef and Andries,1983, Casper, Alapin-Rubillovitz,1985, Shoupe, Montz and Lobo, 1985, Gabriel, Berglund and Simpkins,1986)..

The opiate antagonists may also exert pulsatile PRL release in normal women in late follicular and mid-luteal phases (Cetal, Quigley and Yen,1985) or in women taking oral contraceptive pills (Casper, Bhanot and Wilkinson,1984), but not in hypogonadal women (Quigley and Yen,1980). These evidences suggested the possibility of gonadal steroid in regulation of PRL secretion (Judd, Rakoff and Yen, 1978, Bethea and Yuzuriha,1986, Deis, Leguizamon and Jahn,1988).

The specific cellular effects of morphine and related opiate analogues are not as yet well understood there is no clear cut evdience to relate physical dependent and tolerance development to metabolic activity (Kalra and Gallo, 1983). However, Gaulden et al.,(1964) postulated that morphine and heroin block the transmission of nerve impluses from the median eminence to basal tuberal region of the hypophysis, thus preventing a neurohumoral subtance from reaching the adenohypophysis via the hypophyseal portal circulation. Further studies showed that they may involve other complex mechanism, evidence have been presented which demonstrated that morphine decreases the release of dopamine (Taube, Starke and Borowski, 1977, Deyo, Swift and Miller, 1979, Haskins et al.,1981) and catecholamines (Korf, Bunney and Aghajanian, 1974, Langer, 1981, Kalra and Gallo, 1983). In this regard, a large number of

investigators suggested morphine treatment may result in prevention of a LH surge by decreased influx of norepinephrine excitatory stimuli from presynaptic terminals (Pang, Zimmerman and Sawyer, 1977, Ieiri et al., 1980 Kalra and Gallo, 1983). In morphine-treated rats, sexual behaviour has shown a dose dependent reduction of mount, intromission and ejaculation, this is primarily due to a failure of sexual arousal, but, the effect is different from castration in alteration of dopaminergic metabolism (Clark et al., 1988, Agmo and Paredes, 1988, Mitchell and Stewart, 1990). With repeated use, tolerance develops to the acute positive effects on mood such as increasing apathy, depression and social withdrawal (Mirin and Myer,1978). At the cellular level, the mechanism may involved cyclic adenosine monophoaphate(cAMP) (Sharma et al.,1977), since it has been found that intracellular cAMP levels are lowered when the opiate is given acutely (Klee et al.,1975). On the other hand, longer exposure to morphine stimulate the intracellular cAPM level over a 24 hours peroid (Sharma et al.,1975,1977, Klee et al.,1975, Lampert et al., 1976). If the opiate is withdrawn or naloxone is added, an immediate increase or rebound above baseline levels of cAMP is observed (Sharma et al.,1975). Normalization of cAMP levels after chronic opiate exposure and increment above baseline levels after opiate removal are similar with the phenomena of tolerance and dependence,respectively (Loule, Law and Loh,1986).

The experimental study in rats suggested that opiate dependence could be induced by subcutaneous morphine administration over a period of 5 days (Gibert-Rahola et al., 1988). In monkeys, tolerance to the antinociceptive and rate-

decreasing effect of morphine would developed after 6 week's daily subcutaneous administration of 0.1-3.0 mg/kg morphine for approximately (Craft and Dykstra, 1990), or after receiving intravenous injection of morphine hourly for 6 hours (Krystal and Redmond, 1983). Evidence in man showed that signs of physical dependence develop after giving heroin 4 times a day for 2-3 days(Elliott,et al.,1971).

The reports of withdrawal from chronic opiate administration in humans might be expected to release dopamine from inhibition and reduce serum PRL (Gold et al.,1979). The data from animal study indicated hyperactivity of dopaminergic neurons (Lal,1975, Eidelber,1976) and catecholaminergic neurons (Kantak an Miczek,1988, Valeri,1989) as well as serotoninergic neurons (Kleven and Sparber,1989) in the opiate withdrawal and there has been speculation on the relationship of this hyperactivity to pathophysiology of withdrawal.

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