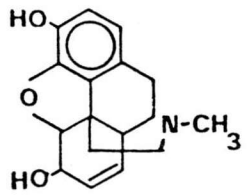
CHAPTER I

INTRODUCTION

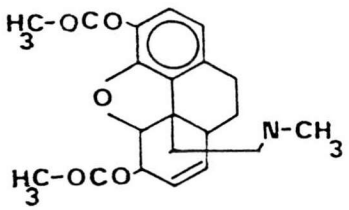
Morphine and related substances from the opium have long been illegally used as the stress reliever and become quite popular among youngsters. Unfortunately, chronic intake of morphine would lead to exert a paramount hindrance on health and economy of the users, their families and eventually to the world as a whole. Although the drug is now still being used in hospital as an effective analgesic agent for treatment of severe pain. Occasionally, they are also used for treatment of diarrhea, cough, anxiety and insomnia (Jaffe and Martin, 1985, Schuckit and Segal, 1987). Major undesirable side effects of continual administration of morphine and the related agents include severe tolerance, physical dependence and addiction (Gaulden et al., 1964, Cushman, 1972, Grossman et al., 1982).

Morphine and related natural plant opiates are a group of alkaloid present in milky juice latex of the unripe seed capsules of poppy plant (Papaver somniferum) named "opium". The alkaloid content constituent can be classified into two distinct chemical classes, phenanthrenes and benzyliquinolines. The principal phenanthrenes are morphine, codeine and thebain, and the principal benzylisoquinolines are papaverine and noscapine (Jaffe and Martin, 1985, Colasanti,1986, Way and Way,1987).

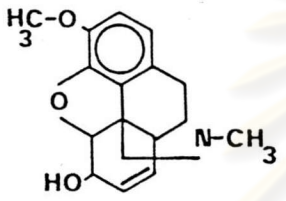
A. Phenanthrenes



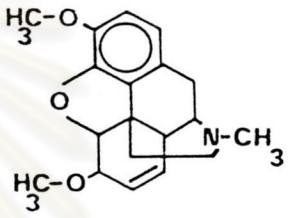
morphine



heroin

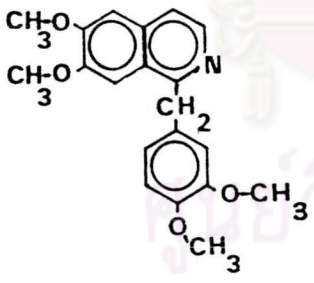


codeine

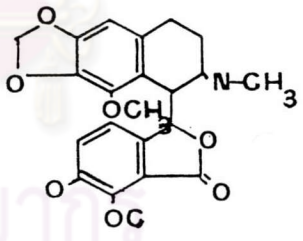


thebaine

B. Benzylisoquinolines



papaverine



noscapine

Figure 1. Chemical structures of major opiate alkaloides, phenanthrenes (A) and benzylisoquinolines (B).

Considerable evidences in the past decade indicated the existence of several endogenous opiates in many mammalian tissues including hypothalamus, adenohypophysis, adrenal cortex,ovaries, testes as well as gastrointestinal mucosae, etc.(Cuello, 1983,

Howlett and Rees,1986, Rosenblatt,1987). These endogenous opiates are a group of active peptide molecules which include endorphins, enkephalins and dynorphin (figure 2).

leucine-enkephalin

Try-Gly-Gly-Phe-Leu

methionine-enkephalin

Try-Gly-Gly-Phe-Met

α-endorphin.

Try-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr

γ-endorphin

Try-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val

leu-Thr

β-endorphin.

Try-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr

Gln-Gly-Lys-Lys-His-Ala-Asn-Lys-Val-Ile-Ala-Asn-Lys-Phe-Leu

dynorphin.

Try-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-leu-Lys-Trp-Asp

Gln-Asn

α-neo-endorphin

Try-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys

Figure 2. Chemical structure of major endogenous opiate peptides. All endogenous opiates share common molecule of amnino acid sequences at 1-4 positions.

High concentration of the opiate peptides and their receptors are present in the vicinity of the median eminence (Blank, Panerai and Frieson,1979, Buckingham and Hodges,1979, Barkan et al.,1983, Herz,1984, Berglund, Derendorf and Simpkins,1988). These opiate peptides interact with the same receptors of the

opiate alkaloids and show similar pharmacological properties in several aspects of neuroendocrine regulations (Meites et al., 1979, Van Vugt and Meites,1980, Ropert, Quigley and Yen,1981, Howlett and Rees,1986)..

In human, chronic addiction of opiates is associated with several reproductive pathologies including amenorrhea, spontaneous abortion and interruption of ovulation (Gaulden et al.,1964, Santen et al.,1975, Quigley et al.,1980, Blankstein et al.,1981). Similarly, symptoms of impotence and decreased libido also occur in men receiving opiates (Cushman,1972, Hellman et al., 1975, Wang, Chan and Yeung,1978). Results of a large series of studies over the past few decades in animal models and chronic addicted cases have shown that acute administration of morphine and related opiate peptides affected inhibitory release of follicle stimulating hormone(FSH), luteinizing hormone(LH) and preovulatory release of LH surge in rats (Bruni et al.,1977, Meites et al.,1977, Kalra and Gallo,1983, Leadem and Kalra,1985b) rhesus monkeys (Spies et al.,1980, Ferin et al.,1982) and women (Mirin et al.,1980, Grossman et al.,1981, Moult et al.,1981, Nappi et al.,1987). In men, suppression of LH secretion followed by a secondary drop in plasma testosterone levels also found in acute and chronic of heroin and methadone administration (Azizi et al., 1973, Mirin et al., 1980). Evidences from several laboratories have suggested that the opiate peptides do not modulate gonadotrophin release at the pituitary site but rather interfere with the tonic release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus (Cicero et al.,1976, Stubbs et al.,1978, Delitala et al.,1981, Lightman et al.,1981, Kalra and Leadem,1984, Thin and Goldsmith,1988). In rats pulsatile the

regulation of LH secretion, via hypothalamic GnRH neurons, is localized in vicinity of ventromedial area (Blake and Sawyer, 1974), a region that also possesses numerous opiate receptor binding site with relatively high concentration of endogenous opiate peptides (Snyder,1975). In addition to the effect of opiate peptides on the hypothalamic- anterior pituitary - gonadal axis, acute and chronic administration of morphine and other opiates clearly lead to prolactin(PRL) release in most mammals, including rodents (Lal,1975, Bruni et al.,1977, Spiegel, Kourides and Pasternak,1982), stump-tail monkeys (Gold, Redmond and Donabedian,1979), cynomolgus monkeys (Settheetham, Varavudhi and Yodyingyuad,1991) rhesus monkeys (Spies et al.,1980) and humans (Von Graffenreid et al.,1978, Reid et al.,1981, Reid, Quigley and Yen,1983). The effect of opiates on PRL secretion may due to reduction of dopamine secretion from dopaminergic neurons into hypophysial portal blood circulation (Gudelsky and Porter,1979, Wardlaw et al.,1980, Demarest and Moore,1981, Lookingland and Moore,1985, Dawood, Khan-Dawood and Romos,1986).

In non-human primates experiments, increase in serum PRL. and cortisol levels are found in association with stress induced infertility. Plasma PRL and cortisol levels in captive group of talapoin monkeys are higher in subordinate monkeys than in dominant monkeys (Bowman, Dilley and Keverne,1978, Keverne,1979, Eberhart, Keverne and Meller,1983). Moreover, subordinate female marmosets are almost always have infertil in the presence of the dominant female (Abbott and Hearn,1978). Indeed exposure to social stress affected on immediate increment of serum adrenocorticotrophin(ACTH) levels followed by a rise in cortisol. The effect may last as long as the stressor is present (Levine

et al.,1970, Brush and Froclich,1975, Manogue, Leshner and Candland,1975, Hennessy,1986)..

Further studies of acute administration of morphine and its analogues in rats indicated that the drug may act as the stressor capable of stimulating acute release of corticotrophin releasing hormone(CRH) from the hypothalamus (Meites et al.,1979, Buckingham,1982, Aguilera et al.,1986), although chronic administration of morphine to rats result in a suppression of the pituitary - adrenal axis and the effect is prohibited by simultaneous administration of an opiate antagonist, naloxone (De Souza and Van Loon,1982, Grossman and Rees,1983). Unlike the rat, acute and chronic morphine injection in human induced inhibition of serum ACTH and cortisol levels (Eisenman, Fraser and Brooks, 1961, Hellman et al., 1975, Ho et al., 1977,. Grossman,1988) and the effect is also reversed by injection of naloxone (Valavka et al.,1979, Morley et al.,1980, Grossman and Besser,1982). However, only one report in chimpanzee failed to demonstrate acute effect of enkephalin analogue on suppression of endogenous ACTH and cortisol secretion (Gosselin et al.,1983).

Endogenous opiate peptides and opiate alkaloids also involve on other hypothalamic pituitary endocrine mechanisms. In man, growth hormone(GH) release in stimulated by an enkephalin analogue (Stubbs et al.,1978, Von Graffenreid et al.1978, Demura et al.,1981) and some exogenous opiates (Delitala,Grossman and Besser,1983). However, the effect on thyroid hormone secretion vary upon species. Opioid peptides inhibit thyroid stimulating hormone(TSH) release in rats (Meites et al.,1979) but stimulate TSH release in men (Stubbs et al.,1978, Delitala, Grossman and Besser,1983).

This present study has been undertaken in adult captive female cynomolgus monkeys(Macaca fascicularis) as a non-human primate model to explore effects of chronic morphine administration upon major reproductive hormonal changes, stresses and related behaviours. Patterns of metabolic turnover of morphine is also followed simultaneously during pre-treatment, treatment and post-treatment intervals. The captive cynomolgus monkey has no breeding season. This monkey also has menstrual cycle length very similar to women (Varavudhi et al.,1982, Zumpe and Michael,1983,1985, Yoshida,1986). Similarly, native free-ranging monkeys in Thailand also exhibited fertile mating in all seasons of the year (Varavudhi et al.,1989). It is hope that this study will provide useful informations for future clinical application.

Aims of the Study.

1. To establish baseline data of metabolic rate of morphine in each monkey during normal pre-treatment cycle as well as during treatment and post-treatment intervals.
2. To study the influence of chronic treatment of morphine on alteration of sexual behaviours.
3. To study long term effects of morphine on alteration of menstrual cycle and associated symptoms including recoveries after drug withdrawal.
4. To follow patterns of serum levels of major reproductive hormones (estrogen and progesterone) and stress hormones (prolactin and cortisol) during pre-treatment, treatment and post-treatment period.