THE USE OF SHORT ACTING NARCOTICS IN OBSTETRIC ANAESTHESIA AND THE EFFECTS ON THE NEWBORN

Thesis

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By

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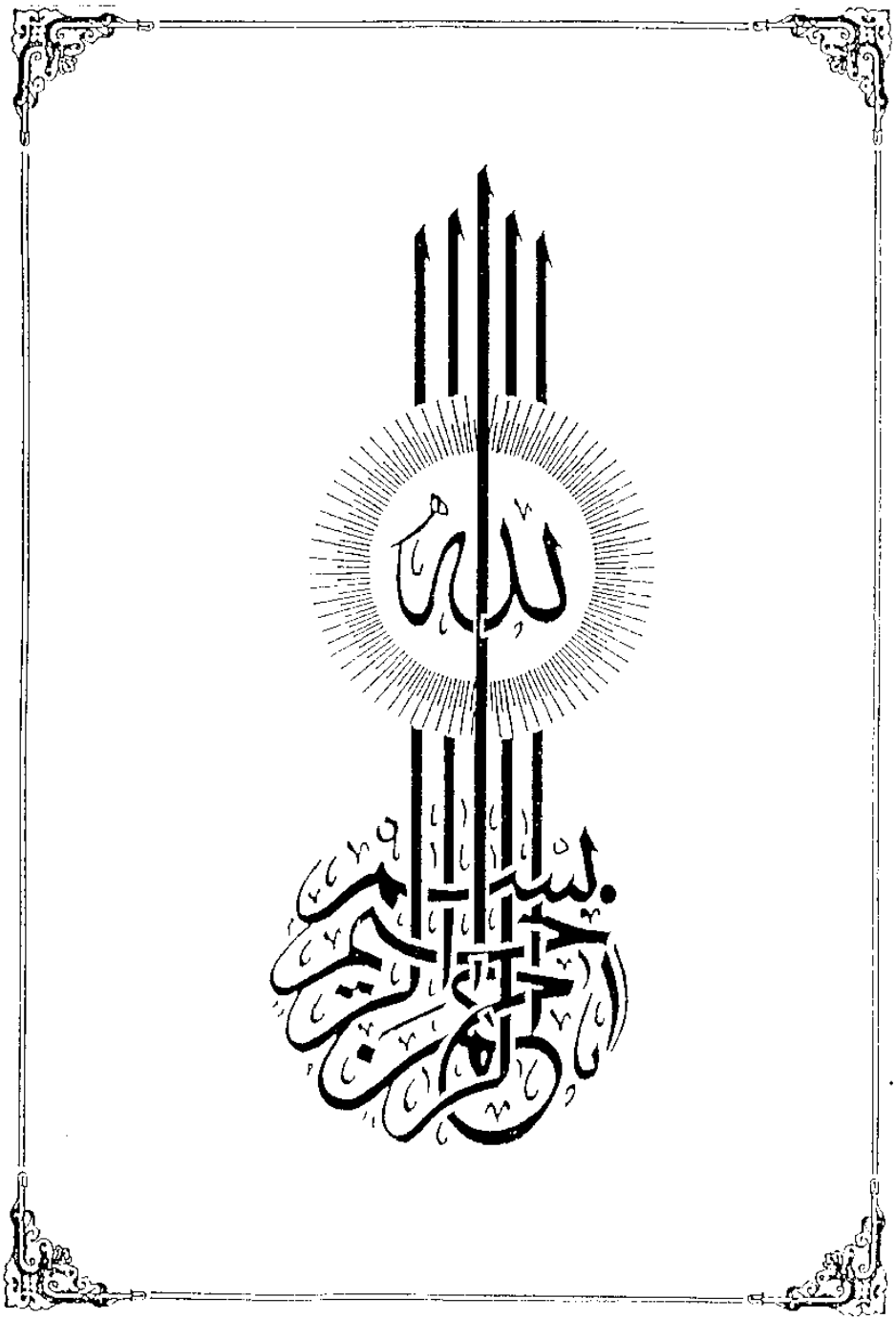
بسم الله الرحمن الرحيم

"سبحانك لا علم لنا إلا ماعلمتنا، أنك أنت العليم الحكيم"

صدق الله العظيم



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INTRODUCTION

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Many elective and most emergent cesarean sections are performed under general anesthesia; however, narcotic drugs are very infrequently used. The usual technique employs thiopental and nitrous oxide with some muscle relaxants. Within the past ten years, small doses of ketamine and subanesthetic concentrations of halogenated inhalation agents have been used successfully. These latter techniques indicate a need for more profound analgesia/anesthesia during operative delivery, and thus a desire to reduce stress that has been shown to have the potential for harmful effects on fetal blood flow and oxygenation.

Narcotic transport studies are limited but indicate substantial differences between the older and newer compounds. Our concern with the use of short-acting opioids in obstetrics must be to determine whether these drugs can be safely used for epidural analgesia during labour, whether they can be used for general anesthesia at cesarean delivery; what their effects are during labor since they easily cross the placenta and what effect they will have on the newborn's neurobehavioral status.

OPIATE RECEPTORS

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Recently there have been major developments in the understanding of the mode of action of opiates. This was initiated in 1973 when three independent laboratories reported the presence of highly specific opiate receptors in central nervous system of vertebrates *(Pert et al., 1973; Jimon et al., 1973; Terenius, 1973).* These receptors combined in a stereospecific manner with all known active opiates and opiate antagonists.

Location of Opiate Receptors (Table 1)

Opiate receptors are concentrated in the periaqueductal grey matter of the brain stem, in the medial thalamus, amygdala, posterior pituitary and substentia gelatinosa of the spinal cord *(Hokfelt et al., 1977).* The cerebral cortex has a low density of receptors and no receptors were found in the cerebellum *(Simon and Hiller, 1978).*

The existence of more than opioid receptors was first postulated by *Martin and his colleagues (1976)* from studies with morphine and some benzomorphan derivatives in spinal dogs. Three receptor types were suggested, mu (μ), Kappa (κ) and sigma (σ), each mediates different spectrum of effects (Table 2).

By far, the most studied receptor type was the mu (μ) or morphine preferring receptor. It mediates a general reduction response to noxious stimuli clinically and in animals including heat, pressure, chemical stimulation or tooth pulp stimulation.

Table 1: Location and functions of opiate receptors (Soloman H. Snyder, 1978).

Location	Function influenced by opiates
I. Spinal cord	
Lamina I & II	Pain perception in the body.
II. Brain stem	
* Substensia gelatinosa of spinal tract of caudal trigeminal.	Pain perception in head.
* Nucleus of solitary tract, nucleus commissuralis, nucleus ambiguns	Vagal reflexes, respiratory depression, cough suppression, orthostatic hypotension and inhibition of gastric secretion.
* Area prostrema	Nausea and vomiting Euphoria.
* Locus coerulus	Euphoria
* Habenula-interpeduncular nucleus, fasciculus retroflexus	Limbic, emotional effect, euphoria.
* Pretectal area (medial and lateral optic nuclei)	Miosis.
* Ventral nucleus of lateral geniculate	Miosis.
* Superior colliculus	Miosis.
* Dorsal, lateral, medial terminal nuclei of accessory optic pathway	Endocrine effects through light modulation
* Dorsal cochlear nucleus	Unknown.
* Para brachial nucleus	Euphoria in a link to locus coerulus.
III. Diencephalon	
* Infundibulum	ADH secretion.
* Lateral part of medial thalamic nucleus, internal and external thalamic laminae, interlaminar (centro-median nuclei, periventricular nucleus of thalamus	Pain perception.
IV. Telencephalon	
* Amygdala	Emotional effects.
* Caudate, putamen, globus pallidus, nucleus accumbeus	Motor rigidity.
* Subfornical organ	Hormonal effects.
* Interstitial nucleus of stria terminalis	Emotional effects.

Table 2: Different opiate receptors and actions mediated through them

	μ	κ	σ
Effects	* Supraspinal analgesia * Respiratory depression * Euphoria * Physical dependence	* spinal analgesia * Respiratory depression * Sedation * Miosis	* Dysphoria * Hallucination * Vasomotor Stimulation
Drugs			
* Morphine	Ag.	Ag.	
* Nalbuphine	pAg/Ant.	Ag.	Ag.
* Bupernorphine	pAg.		
* Nalorphine	Ant.	pAg.	Ag.
* Pentazocine	Ant.	Ag.	Ag.
* Butorphanol		Ag.	Ag.
* Naloxone	Ant.	Ant.	Ant.

Ag = Agonist

Ant. = Antagonist

pAg = Partial Agonist

(Quoted from Joff, J.H. and Martin, W.R., 1980) Opioid analgesics and antagonists. In Gilman, A.C. Goodman, L.S., A. (eds.). The pharmacological Basis of Therapeutics (ed. 6) chapter 22, New York, Macmillan, 494-534.

It also causes bradycardia, miosis and indifference to environmental stimulation. Proposed (μ) receptor agonists produce morphine like tolerance and dependence and can substitute morphine in dependent animals. μ receptors are activated by morphine, B-endorphin, metenkephalin or enkephalin analogues *(Cacel et al., 1981).*

Activation of Kappa (κ) receptor produces miosis and sedation rather than indifference to environmental stimulation. Ketocyclazocine and ethyl-ketocyclazocine were proposed as (κ) agonists. They reduce spinal responses. They do not substitute for morphine in dependent animals and produce physical dependence and a withdrawal syndrome which is distinct from that produced by (μ) agonists *(Cow and Fisher, 1984).* Whether κ-receptor can also

mediate clinical antinociception, it was reported that in animal models, κ-receptor agonists are active in writhing, paw pressure and teeth pulp stimulation tests, in all of which μ-agonists, κ-receptor agonists are ineffective against thermal pain except at doses producing sedation and motor impairment *(Tyers, 1980).*

The (σ) receptors are not proposed to be associated with a reduced response to noxious stimuli, but their activation is associated with mydriosis, tachycardia and psychomimetic actions of many opioid derivatives. A typical agonist at σ-receptor was N-allyl-norcyclazocine (SKF 10047). Similar hallucigenic effects are seen with phencyclindine group of drugs. The effect of phencyclindine is mediated by a stereospecific receptor site which is known as (PCP) receptor *(Zukin and Zukin, 1979).*

The binding of SKF 10047 in brain is a complex and exhibits at least two component. The high affinity component which can be blocked by morphine and represent μ-receptor. The low affinity site which can be blocked by phencyclindine *(Zukin, 1982).* It may be that the σ-receptor is composite opioid-PCP receptor.

The agonist for the σ-receptor appears to be Leu-enkephalin. In addition pentazocine or other agonist antagonists may be examples for drugs that act preferentially at σ-receptor. There is likely cross-reactivity in vivo between μ and κ receptor agonism of "selective" lignades *(Van Ree et al., 1979).* The main role of σ receptor is apparently that of modulating μ-receptor.

Vaught et al. (1982) proposed the dual receptor complex theory which illustrated that morphine and σ-receptor exist as a complex when morphine or an agonist for μ-receptor interacts with that receptor which ultimately

produces analgesia. The role of σ-receptor in this complex is not to produce analgesia, but rather to modulate the activity of the coupling mechanism. Conceptually Leu-enkephalin are agonists to σ-receptor, interacts with that receptor and facilitate the coupling mechanism of μ-receptor with its effector producing analgesia.

Pasternak (1982) examined the possibility that analgesic activity of both μ and σ-agonists might be mediated through the same receptor site. He further subdivided the μ-receptor into those with high affinity (μ_1) and those with low affinity (μ_2). Under this classification analgesia was associated with (μ_1) and not with the low affinity μ_2 and σ-receptors. The evidence produced by earlier workers *Kosterlitz et al., 1980 and Ronai et al., 1981* also suggests that σ-receptor do not mediate analgesia.

The rat vas deferens perforation yielded yet, another opioid receptor the ε-receptor. On this preparation the responses to electrical stimulation are blocked by B-endorphin. However, the responses of this tissue are not blocked by morphine and are resistant to the stable enkephalin analogues *(Schulz et al., 1981).*

The rat vas deferens is the only preparation to exhibit this receptor type and it is interesting to note the κ-agonists are antagonists to the action of B-endorphin in this tissue. Morphine and related opioids are thought to exert their agonistic action primarily at the μ-receptors and to lesser degree at the κ-receptors *(Martin et al., 1976).*

Agonist-antagonists presumably bind to the μ-receptors and can therefore compete with other substances for these sites, but either they exert no actions (i.e., they are competitive antagonists) or they exert only limited

action (i.e. they are partial agonists) at μ-receptors. They also may exert agonistic action at the κ and σ-receptors *(Jaffe and Martin, 1980).*

Agonist-antagonists appear to act as partial agonists at one receptor type or another. Such drugs exhibit a ceiling effect i.e., their maximal effect is less than that produced by strong agonist when there are low levels of physical dependence, but they precipitate withdrawal symptoms in subjects who are dependent on a high level of strong agonist *(Martin, 1976; Jasinki, 1979 Jaffe and Martin, 1980 and Lewis, 1980).*

Huges (1975) demonstrated the ability of brain extracts to mimic morphine's effect on smooth muscle preparations such as the mouse vas deferens and guinea pig ileum. He identified two pentapeptides which had opiate activity in the brain of the pig. These were methionine enkephalin "Metenkephalin" (tyrosine-glycine-glycine-phenylalanine-methionine) and leucine enkephalin" Leu-enkephalin" (tyrosine glycine-glycine-phenylalanine-leucine) which differ only in their terminal carboxy amino-acid. It was noted that the pentapeptide methionine enkephalin was found within a much larger protein molecule called Beta-lipotrophin. It was isolated from the pituitary by *Li (1964)* and was referred to as a minor component of pituitary extract *(Guillemin et al., 1977).*

Beta lipotrophin has 91 amino-acid residues. The residues 41-58 constitute B-melanocyte stimulating hormone. It was recognized that 61-65 amino-acid sequence of Beta lipotrophin was identical with met-enkephalin. Another polypeptides larger than the enkephalin and have the opiate activity were extracted from pigs by *Ling, Burgus and Guillemin (1976).* All contain methionine-enkephalin at their N-terminals. They are fragments of Beta-lipotrophin. These polypeptides are α-β-γ endorphins. Endorphin is a

generic term that is applied to all endogenous peptides with opioid activity. These substances correspond to amino-acid sequence 61-76, 61-91, 61-77 and 61-87 of Beta lipotrophin respectively. Endorphin is also termed the fragment of Beta lipotrophin. The most potent fragment is the terminal 31 amino-acid of Beta lipotrophin which corresponds to β-endorphin. On injection of Beta-endorphin in the third ventricle of the rat, it proved to be a stronger analgesic than morphine *(Feldberg and Smyth, 1976)*.

Beta-endorphin appeared to account for virtually all the opiate-like activity of pituitary gland which is devoided of enkephalin *(Simantove et al., 1977)*. Beta-endorphin is not a source of brain encephalins since removal of the pituitary fails to alter brain content of enkephalins *(Goldstein, 1976)*. Therefore, it is likely that Beta-endorphin is a pituitary hormone released in blood *(Guillemin et al., 1977)*.

Studies of the biosynthesis of adrenocorticotrophin (ACTH) have demonstrated a remarkable link to Beta-endorphin. ACTH contains 39 amino-acids and has a molecular weight of about 4000. It is synthesized by cleavage from larger precursor peptide which is referred to as big ACTH. The latter has been shown to contain as a part of its amino-acid composition the entire sequence of β-lipotrophin as well as ACTH *(Mains et al., 1977; Roberts and Herbert, 1977)*.

Thus ACTH and Beta-endorphin are the parts of the precursor. These findings coincided with the independent observation that ACTH, Beta lipotrophin and Beta-endorphin are stored in the same cells which are highly concentrated in the intermediate and anterior lobes of the pituitary gland *(Moriarty, 1973 and Bloom et al., 1977)*.