THE ROLE OF THE PITUITARY REGION IN THE ENDOGENOUS PAIN CONTROL MECHANISM

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PROEFSCHRIFT

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DINSDAG 4 MEI 1982 DES NAMIDDAGS
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dank voor alles

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PREFACE

It is often difficult to come to grips with the phenomenon of pain. It is still impossible with any degree of elegance, to combine together under one single theory all our knowledge of pain prevention, and all the factors that play a role in pain perception. Indeed, the very definition of pain presents problems and causes a furore of discussion. Muskey and Spear (1967) described pain as an unpleasant experience associated with damaged tissue, or described in terms thereof, or both. Fordyce (1978) adds an extra dimension to this observation asserting that one can only speak of pain when it is accompanied by a visual or audible comment on behalf of the patient.

The concept of pain attracts the attention of everyone who works in medicine, as he comes into contact directly with patients who are suffering pain. Every doctor or member of the ancillary medical services, indeed even the 'man in the street', is daily confronted with pain sufferers. Science of pain is therefore not confined to one specialty but is to be approached from various disciplines, such as anatomy, neurophysiology, biochemistry, psychology, and philosophy.

Members of all these specialities contribute pieces of the puzzle, but none has yet been able to fit them together to give a comprehensible picture of the whole of the pain phenomenon. A multidisciplinary approach to the patient is therefore unavoidable and the function of pain treatment teams, with members drawn from many specialities, is therefore a very suitable approach, particulary when dealing with the chronic pain patient. The possibility of admitting to hospital, and evaluating patients with pain, a possibility that is only to a very limited extent present in the Netherlands, should be firmly built into any health service.

This thesis consists of no more than another piece of the puzzle that fits together with other pieces contributed by other workers in this field. It is limited to an anatomical and physiological model in which the central place is not taken by man but by an experimental animal. It is hoped that it may open the way for a new clinical treatment modality for the patient with chronic unbearable pain.

INTRODUCTION

Removing the cause of pain is impossible in many patients and this is particulary so in patients with pain caused by a malignant disease. It is very important to attempt treatment in cancer patients because the pain can be so intense and unbearable that it appears as the leading subjective symptom in the clinical course of the disease.(1)

Treatment of intractable pain in patients with a short expectation of life, however, seems to be more successful than in patients without cancer. 85% of those having unilateral pain in spinal dermatomes were painfree after treatment until they died. In patients with bilateral soft tissue or bony tumors, treatment of pain was successful in 75%.(2)

A development of drug addiction to narcotics and interference with the quality of life are complications of pain therapy. Nowadays, however, it is possible to avoid habit forming-narcotic drugs.

Some of the techniques available in pain treatment will be briefly mentioned.

Analgesic Drugs

a. mild analgesics (a group of drugs like asprin)

b. intermediate analgesics (like Pentazocine)

c. narcotic drugs:

The possibility of producing a clouding of consciousness or addiction to the drugs should be borne in mind - indeed complete character or personalty change may occur in the patient.

d. addictive anxiolytic drugs:

Treatment of anxiety and agitation, present in patients with neoplasia is in many cases indicated and an adjuvent drug can produce a more successful relief of pain.

Radiotherapy

When using this technique in order to relieve cancer pain, response is mostly observed within about two weeks; however, in exceptional cases relief occurs later.

Chemotherapy

This therapy should be stopped if there is no improvement within about three weeks, because this kind of treatment often produces unpleasant side effects.

Cervical cordotomy

An anterolateral tractotomy in order to section the ascending pain pathways can be performed directly by a surgical procedure or

indirectly by a percutaneous route. By sectioning the antero-lateral tract, pain is relieved on the opposite side of the body without loss of sensation. It is particulary suitable for unilateral cancer pain below the fifth cervical dermatome. After an interval, however, the pain perception returns.

Nerve Blocks

Nerve blocks can be performed peripherally or centrally with long-acting 'local anaesthetic-solutions' to produce analgesia in a particular region of the body. Before injection of destructive solution the expected result should be confirmed by employing a short acting local anaesthetic agent. When employing nerve blocks it is not uncommon for the patient to experience a similar pain in another area after the dominant pain has been suppressed. This forces the therapist to perform one block after another.

Electrical Stimulation

This method is based on the theory that large nerve fibres in the posterior columns modify the appreciation of pain. Stimulation of the columns can be performed transcutaneously or surgically by implantation of the electrodes directly in the region of the posterior columns.

Acupuncture

It is not our intention to discuss the mechanisms of this kind of treatment in producing analgesia or even anaesthesia. Research in this field is being carried out in many investigation centres and its value is being assessed especially in non-malignant pain.

Hypophysectomy

It is necessary to make a difference between the surgical hypophysectomy and the method of injecting alcohol into the sella turcica as introduced by Moricca. He called this technique "chemical hypophysectomy". Later on the term was changed to "neuroadenolysis of the pituitary gland" - (NALP). However, with the gap in knowledge about the mechanism which leads to pain relief, we have to be careful in the use of this term for the procedure of injecting alcohol into the sella turcica, because it suggests a mode of action which is very doubtful. The so-called "neuroadenolysis of the pituitary gland" will be discussed in detail.

PART 1

CHAPTER 1

Survey of the literature of "neuroadenolysis"

1.1 History

"Chemical hypophysectomy" for relief of intractable cancer pain in patients has been described since 1968. (Moricca 3, 4, 5, 6).

The technique originated from the observation that pain due to hormone-dependent tumors and their metastasis can regress with hormone-subtractive surgical treatments like orchidectomy, ovariectomy, adrenalectomie or hypophysectomy. The surgical treatment by attacking the pituitary gland function has already been described by Olivecrona as early as 1953.(7) The search for other techniques as a replacement for surgery has been done applying roentgen therapy, ultrasonic destruction and diathermocoagulation by transfrontal approach. Most of these techniques were inadequate for inhibiting a normal functioning pituitary gland or had an increasing effect on the incidence of accidents and complications. "Chemical hypophysectomy" by injecting a neurolytic agent like alcohol in the sella turcica proved to be very effective in treatment of intractable cancer pain, not only for pain caused by hormone dependent tumors but also for nonhormonal dependent neoplasias.

1.2 Result

Moricca described the results of treatment of 687 patients - in total 1593 "adenolysis procedures" were performed. Most patients had visceral or bony associated metastases, and in many cases the patients were in a very poor condition.

Only one patient did not benefit at all, 12 showed a very good improvement, but not complete relief, and in 69 patients complete relief from pain was produced after the second injection. In 605 cases pain relief was complete, immediate and long-lasting. The results 'exceeded every expectation showing to be extremely effective in relieving any kind of neoplastic pain, both caused by hormone-dependent and non-homone-dependent tumors. In fact, the pain resolves independently of the further evolution of the neoplastic disease.(6)

However, as shown in the recent world congress on "alcohol adenolysis of the pituitary gland" in Verona (June 1981) the success rate in relieving intractable cancer pain in this way varies between 40 and 90%. This variation was not attributable to the different techniques used by the various investigators. At first it was more influenced by patient selection. Another point of interest was the question - How did the evaluator define the result as successful?

For example; some investigators define a reduced use of morphine as success while others judge the treatment as unsuccessful if the patient still needs a narcotic drug. This is only one example while it is possible to enlarge the summary of these for many reasons. It was therefore, suggested by Lipton during the world congress (1981) that a worldwide accepted protocol of evaluation should be instituted. Furthermore, the incidence of complications due to the procedure of "NALP" is not clear in the published work.

Rhinorrhea with bacterial meningitis has been reported.(8) Other complications were ptosis diplopia and hemianopsia in small percentages. In the serie of J. Katz, one patient needed a treatment with penicillin and operative intervention was necessary to stop the cerobrospinal fluid leak - the floor of the sella was repaired with alpha-ethyl cyano acrylate. Moricca's published work describes the complications as self limiting and minor.(6)

Other kinds of compliations are those which are directly linked to the wounding of the pituitary gland or to a possible destruction of the hypothalamic pituitary axis, as; diabetes insipidus, hypoadrenalism, hypothyroidism, and lowering of libido. Most investigators described these complications as 'usually self limited' or easily treatable with hormonal replacement.

Yanagida observed in 50% of his patients, after "NALP", a reduction of hormonal levels of L.H. (Luteinotropic); FSH (follicle stimulating); GH (growth hormones) and a decrease of the level of 17 KS (17 Ketosteroids); 17 OHCS (oxyhydrocorticosteroids) and prolactin. In the remaining 50% no change of these hormones occurred. It must be noted that no correlation was observed between pain relief and hormonal behaviour following the procedure of alcohol injection into the sella turcica.

1.3 The technique of "neuroadenolysis"

Most investigators use neuroleptanesthesia combined with a muscle relaxant and a mixture of N20-02. Low concentrations of a gas like halothane are added to the anesthesia mixture for maintenance.

Neuroleptanalgesia has been advocated because it allows the operator to monitor eye movements during the injection.(6)

In all described procedures an orotracheal tube is inserted to insure an adequate airway or to have the possibility of mechanical ventilation.

J. Katz et al(8) use a Todd-Wells stereotaxic head holder and after using a drill in order to make a hole in the floor of the sphenoid sinus a 6 inch 20-gauge spinal needle is gently inserted through a needle guide into the floor of the sella turcica. The position of the needle is checked by X-ray. Most investigators, however, insert the needle (16 gauge, 14 cm stainless-steel needle containing a stylet) directly through the nostril close to the nasal septum, and by gently hammering on the hub of the needle a stepwise advancement through the sphenoid bone and the floor of the sella is accomplished. The progression of the needle is monitored continuously using biplane x-ray control.(1 6 9)

Moricca uses two or more needles in many cases to be sure that the neurolytic agent becomes deposited in different areas and at different depths in the sella.

In the literature this variation is between 2 and 8 ml alcohol. The agent is injected in 0.1 ml and 0.3 ml increments over a period of 3 to 5 minutes during which time the pupils are continuously checked with a light source. Sudden pupillary dilation can be a sign of involvement of the optic tract or tracts.

Further injection of neurolytic agent is stopped until the pupil (or pupils) return to normal size, and after that, a further injection is carefully performed until the total amount has been injected.

Katz et al deposited 2 ml of alcohol at various depths by changing the position of the needle within the sella turcica.(8)

1.4 Theoretical Basis

How the procedure, originally described by Moricca, relieves the cancer pain is still uncertain.

Several theories have been discussed to explain the responsible mechanisms. Interference with hormonal regulation may be a factor. However, treatment of patients with nonhormonal tumors has the same result as in patients with hormone dependent neoplasias.

Another explanation can be that, besides chemical destruction of the pituitary gland an interruption of pain pathways occurs. Studies involving injections of contrast media into the sella turcica of cadavers have shown that the injected fluid may spread beyond the hypophysis with possible effects on the surrounding structures.(10)

It has also been suggested that endorphins are important. Removal of pituitary gland endorphin production may cause a compensatory overproduction of brain endorphins, but Misfeldt et al, however, showed that it was impossible to reverse the analgesia following "hypophysectomy" by naloxone.(11)

Yanagida and Corssen working in rats found immediate and sustained falls of beta-endorphin levels in the whole brain and in certain separate brain regions, including the midbrain, hindbrain, cerebellum and the hypothalamus, while beta endorphin concentrations were unaffected in thalamic, subthalamic and hippocampal regions. The cortex beta-endorphin levels however, increased temporarily during the first five days following hypophysectomy and decreased thereafter below the original level.(12)

They also investigated the evoked potential response after electrical stimulation of the tooth pulp in rhesus monkeys from the somatosensory cortex, and centrum medianum of the thalamus and the midbrain reticular formation before and after injection of absolute alcohol into the sella turcica and again following administration of naloxone. A marked decrease in amplitude of evoked potential was observed in all investigated areas; naloxone only reversed the "NALP" induced changes of tooth pulp evoked potentials in the primary somato-sensory cortex of animals following complete destruction of the pituitary gland.(9)

These findings suggest that interference with sensory pathways, produced by injection of alcohol, may be a causative factor in the pain relief.

The purpose of the present study was to determine neuronal activity of the pituitary region and the influence on it of alcohol injection into the sella turcica and the influence on this activity of an intravenous application of naloxone with the hypothesis that the pituitary region has an inhibitory effect upon the pain response in the sensory cortex.

The next questions that arise are:

1. What is the effect of alcohol injection into the sella turcica on TPEPs.
2. What is the effect of naloxone before and after alcohol injection into the sella turcica on the reponse of the pituitary region in comparison to the somatosensory cortex.

In the following, the term pituitary region (PR) is defined as the region that includes the adenohypophysis, the stalk, and the recessus infundibularis.

Furthermore, we assume that the adenohypophysis is not involved in the mechanism of the immediate pain relief after injection of alcohol into the sella turcica.

CHAPTER II

Experimental work on the role of the Pituitary Region (PR) in endogenous pain control of the monkey related to Neuroadenolysis

2.1 Methods

Three adult rhesus monkeys (maccaca mulatta), weighing 4 to 8 kg each, served as experimental animals. Electrical stimulation of the tooth pulp was chosen as somatic pain stimulus because this stimulus represents objective, quantifiable, nonverbal means of producing central nervous system response interpreted as pain.

Under ketamine anaesthesia, two stainless-steel bone screws were placed on the primary somatosensory cortex (PSC); an area from which TPEPs could be expected to be recorded. A 16-gauge, 14 cm stainless-steel needle containing a teflon-coated stainless-steel wire electrode with a hook at the tip was inserted through either the left or right nostril and advanced in close proximity to the nasal septum. The advancement of the needle through the sphenoid bone into the floor of the sella turcica was accomplished by gently hammering on the hub of the needle. Progression of the needle was carefully followed by biplane fluoroscopy until the tip had reached its final position in the center of the sella, aligned precisely in

the midline. The teflon-coated stainless-steel wire electrode was kept in this position due to the hook at the tip while the needle was thereafter removed.

TPEPs were recorded from the pituitary region between the tefloncoated stainless-steel wire electrode in the pituitary region and one stainless-steel bone screw placed in the midline of the frontal skull.

All electrodes and bone screws were connected by insulated connecting wires to a plastic multipolar plug and were secured to the skull with dental acrylic. For application of the pain stimulus small holes were drilled through the enamel and dentine of the right or left maxillary incisor to a depth of about 1,5 mm, through which two self-threading, stainless-steel pins were placed into the tooth pulp. The pins were soldered to insulated connecting wires which were passed subcutaneously to the multipolar plug as described.

The exposed junctions of the dental pins and steel wires were insulated from the oral cavity by self-curing dental acrylic. Following the implantation of the electrodes, the monkeys were allowed to recover for 3 days.

Recording sessions were conducted in a darkened room with the unsedated monkey placed in a restraining chair in the upright position. AC-amplifiers of the polygragh recorder system (Grass) were employed to amplify the potentials and a Hewlett Packard storage oscilloscope was used for monitoring. Stimulus and evoked potential response of the somatosensory cortex and the pituitary region were continuously registered on the different channels of the grass recorder. Averaging of the evoked potentials was accomplished with

a Didac 800 (intertechnique) clinical averager. Permanent records of the averaged potentials were obtained by means of an onmigraphic X-Y plotter.

Square waves were generated by an electrical stimulator (Grass S28) with modified stimulus isolation and constant current. Analysis times were 100 msec. The responses to 25 consecutive stimuli administered to each animal were averaged. Initially, responses to stimuli were averaged for 100 msec following 25 consecutive stimuli and the mean of the voltages computed during this period was used as baseline.

Amplitudes were measured from the base to the peak of each component wave. The electrical stimuli consisting of monophasic square waves of 0.3 msec duration and 5 volts were delivered at 3.0 second intervals bipolarly across the pulp cavity.

A single dose (0,008 mg,kg) of naloxone was administered intravenously and subsequently all measurements were repeated. After these recordings the monkeys were subjected to injection of alcohol into the sella turcica in the way as previously described. TPEPs were recorded again, before and after naloxone, after a period of 36 hours in the fully awake monkey.

An intravenous catheter and an intra-arterial catheter were introduced to arterial and vena femoralis by atero-veno section. The catheters were fixed by suture to the skin and thereafter a cast was applied to the upper and lower leg thus stabilizing and securing the catheters.

The venous catheter served for intravenous glucose electrolyte infusion supplemented with ketamine for continuous intravenous ketamine anesthesia, and for injection of naloxone.

Via the arterial catheter continuous blood pressure control was performed and bloodgas and electrolyte control done intermittantly. For the introduction of the hypophyseal needle placed into the center of the PR, the monkey was intubated without relaxation and maintained at spontaneous respiration.

The experiments were thus performed in two steps. First, placement of electrodes including PR electrode as described above followed by recording of normal physiological values; and second, introduction of a needle into the sella turcica via the other nostril, and injection of alcohol with therafter recordings of post "NALP" parameters.

2.2 Results

2.2.1 Behavioural Findings

There was no indication in any one of the three monkeys that the chronic implantation of recording electrodes into the skull bone, and into the PR, and placement of stimulating electrodes into the tooth pulp as well as the injection of alcohol into the PR resulted in behavioural changes. Rejection behaviour, anger, appetite, attentiveness, and spontaneous body movement were unchanged.

2.2.2 EEG Response

Before stimulation, the normal EEG was recorded. In the cortex a normal EEG with clear spindle bursts was monitored, which means

that a normal, not excited, very settled animal in an awake state was present. The pituitary region activity showed a high voltage, slow activity.

After recovering from alcohol injection into the sella turcica the behaviour of the monkey showed no changes: cortical EEG was the same with just the spindle bursts a little increased. Slowing of the EEG pattern was the only change in pituitary region activity (fig 1).

Intravenous injection of naloxone after alcohol injection, on the contrary, changed the EEG totally. An increase of low voltage fast activity in the cortex and a rythmic high voltage activity in the pituitary region appeared (fig 2).

2.2.3 Tooth Pulp-Evoked Potentials (TPEPs)

1. Primary Somatosensory Cortex (PSC)

Before "NALP", triphasic responses to tooth pulp electrical stimuli were observed in the recordings obtained from the PSC. In all animals, the tracings from the PSC showed a characteristic initial steep negative deflection of the potential, followed by a double positive deflection. The amplitude of the second positive wave with an approximately 30 msec delay after stimulation seemed to correspond with the intensity of the stimulation. After injection of naloxone, the second positive wave showed a significant increase in amplitude and a significant increase of the delay to more than 25 msec (fig 3). After injection of alcohol into the sella turcica, the second positive wave disappeared totally.

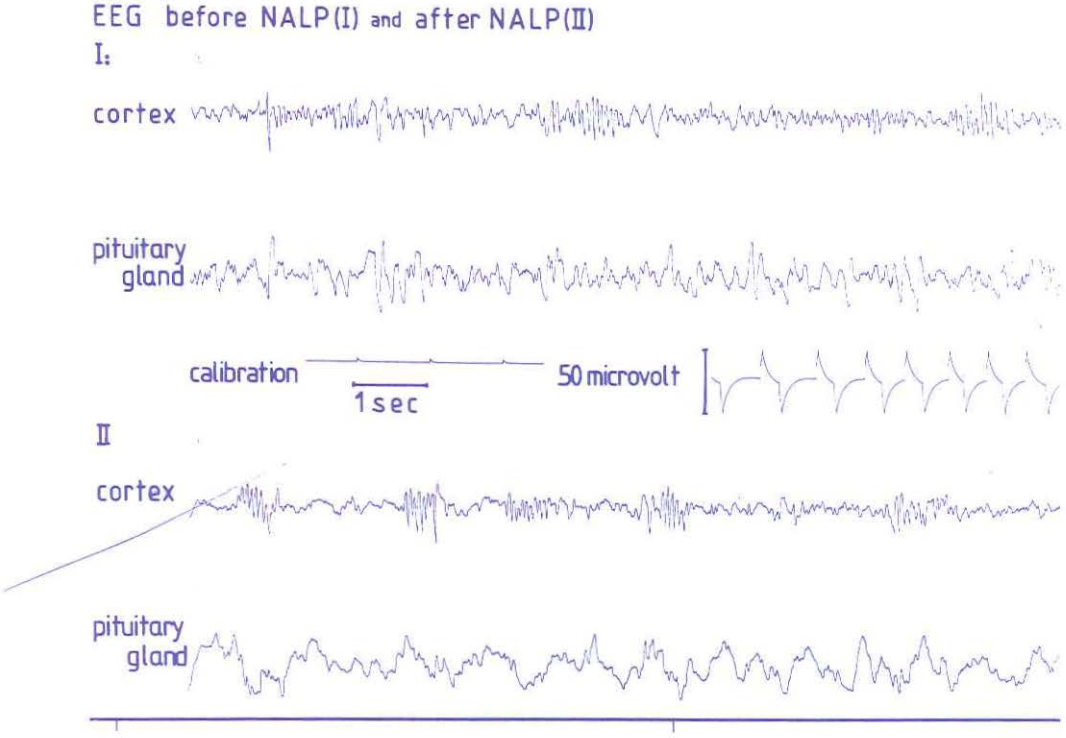
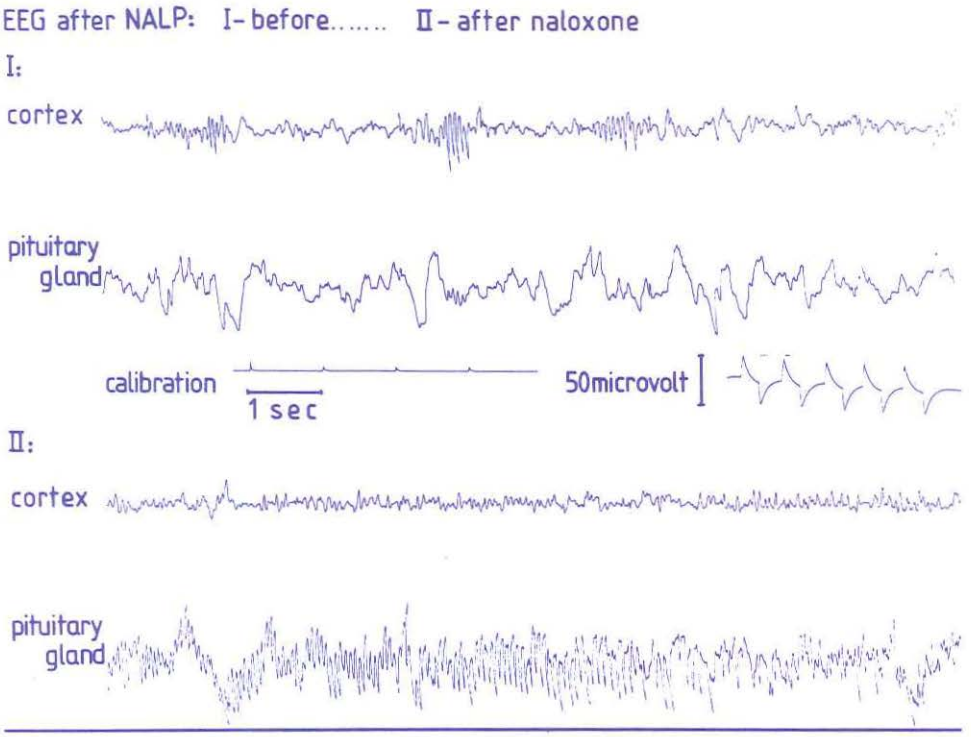


FIG. 1: THE INFLUENCE OF THE ALCOHOL INJECTION INTO THE SELLA TURCICA ON THE E.E.G. OF THE CORTEX AND ON THE E.E.G. OF THE PITUITARY REGION.



.FIG. 2: THE INFLUENCE OF NALOXONE ON THE E.E.G. OF THE CORTEX AND ON THE E.E.G. OF THE PITUITARY REGION AFTER THE INJECTION OF ALCOHOL INTO THE SELLA TURCICA.

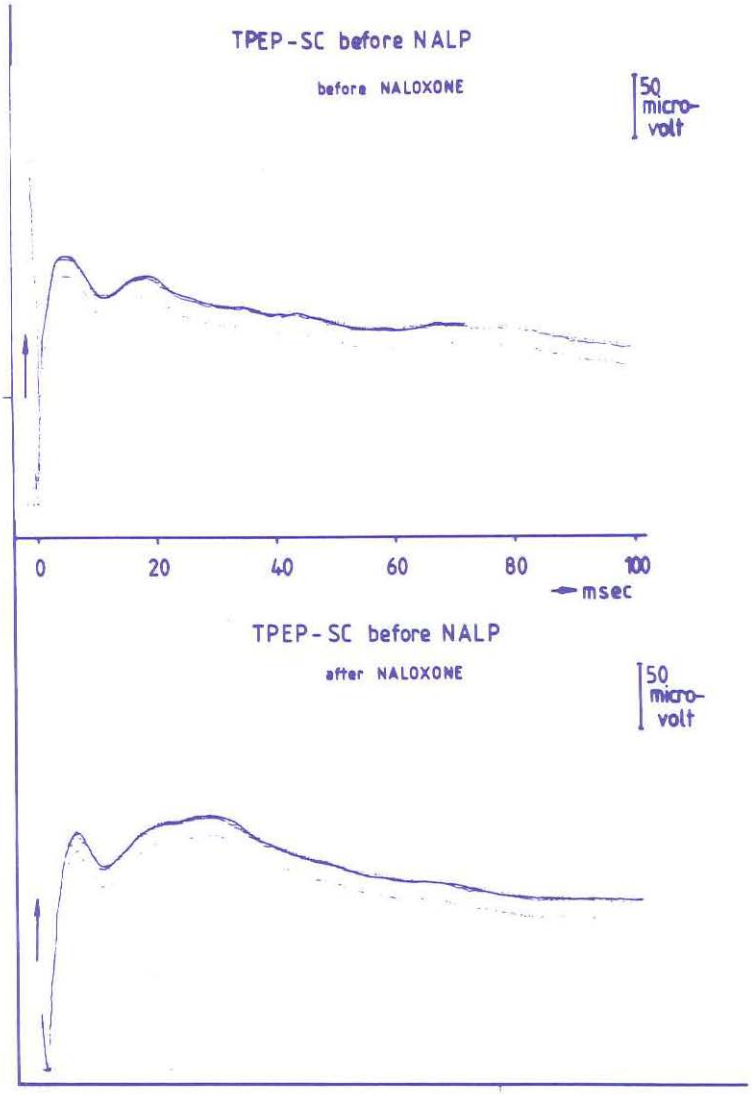

TPEP-SC before NALP
before NALOXONE
50 micro-volt
0
20
40
60
80
100
msec
TPEP-SC before NALP
after NALOXONE
50 micro-volt

FIG. 3.

Injection of naloxone after "NALP" was followed by reappearance of the second positive wave nearly to the same shape as it was seen in the PSC before "NALP" (without naloxone), (fig 4).

2. Pituitary Region

Before "NALP", polyphasic responses to tooth pulp electrical stimuli were observed in the recordings obtained from the pituitary region. The tracings from the pituitary region showed a characteristic initial steep negative deflection of the potentials followed by a biphasic steep positive deflection and thereafter smooth slow potential waves. The amplitude of the second steep positive potential seemed to correspond with the intensity of the stimulation. After naloxone injection, the second steep positive potential was slightly but not significantly decreased while the latency was unchanged (fig 5). "NALP" induced a significant increase of the secondary steep positive potential, after naloxone this potential was severely decreased with unchanged latency,
(fig 6). This was in contrary to changes in the PSC where the original response reappeared after injection of naloxone (fig 4).

2.2.4 Histological Findings

Monkey I: There was a small area of spongionecrosis in the recessus infundibularis with a very slight haemorrhage and a depletion of the ependym epithel. The nuclei of the stalk neurones were in a slight spongy state. The hypothalamus showed no changes.

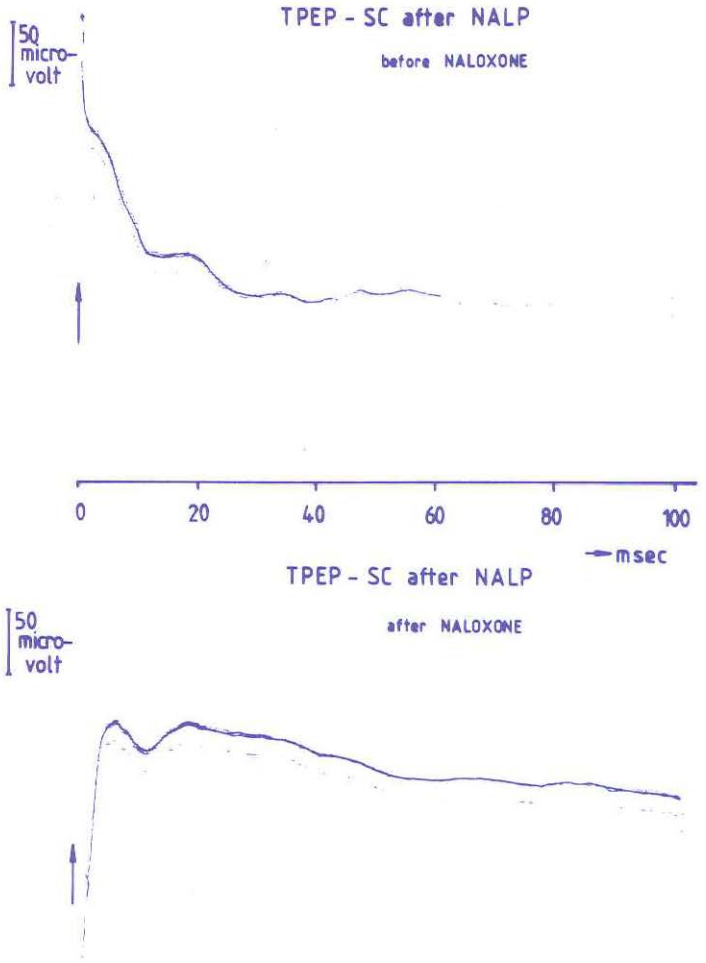

TPEP - SC after NALP
before NALOXONE
50 micro-volt
0
20
40
60
80
100
msec
TPEP - SC after NALP
after NALOXONE
50 micro-volt

FIG.4.

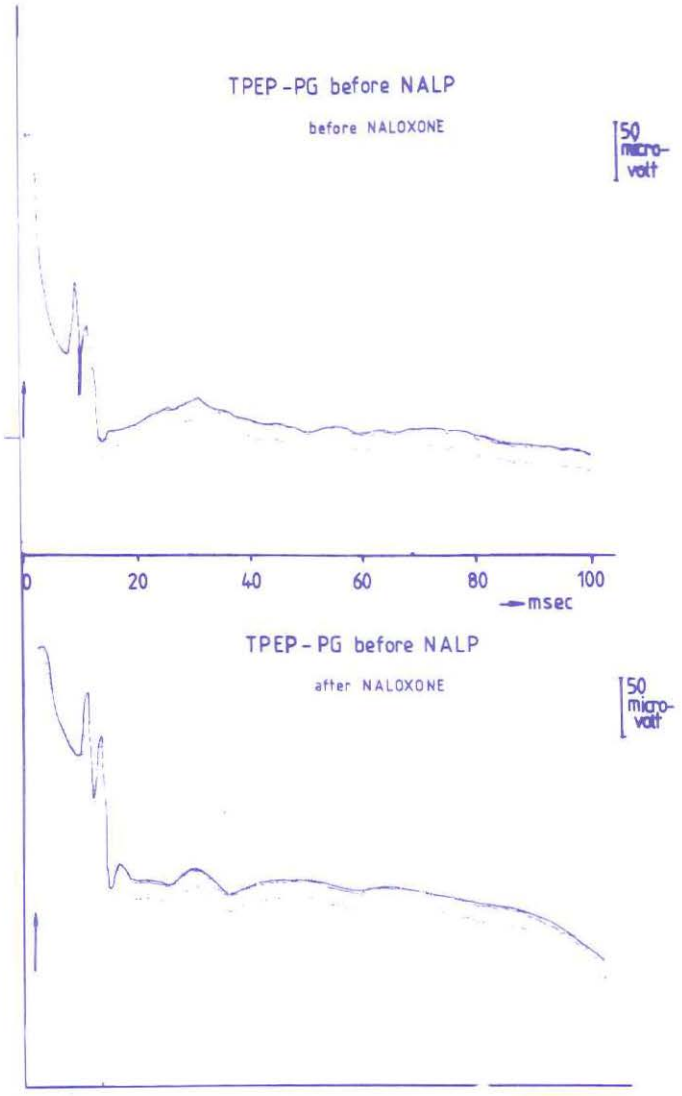

TPEP-PG before NALP
before NALOXONE
50 micro-volt
0
20
40
60
80
100
msec
TPEP-PG before NALP
after NALOXONE
50 micro-volt

FIG.5.

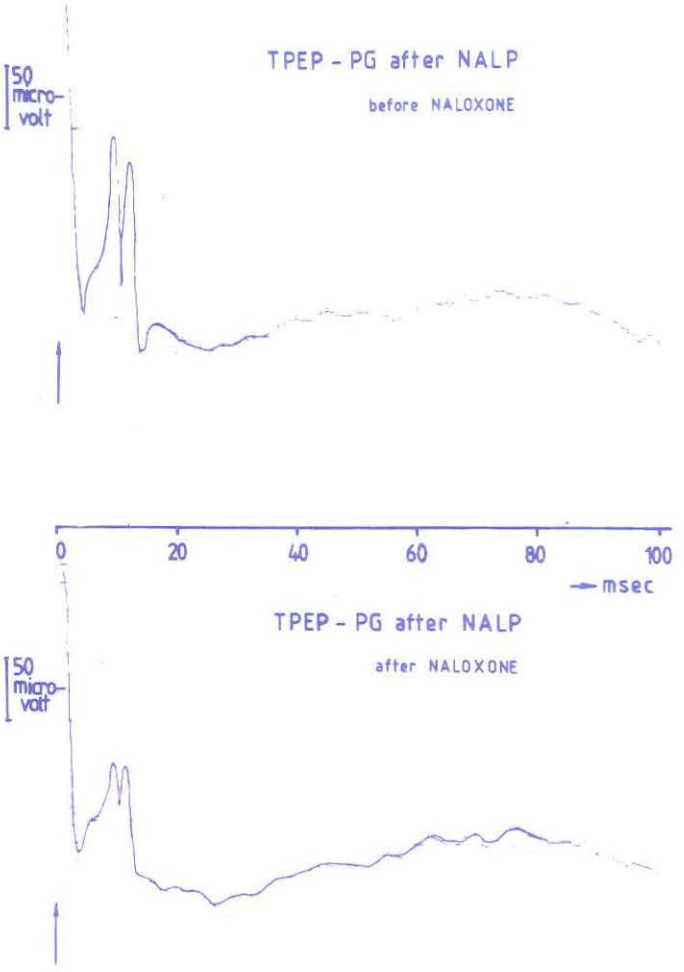

TPEP - PG after NALP
before NALOXONE
50 micro-volt
0
20
40
60
80
100
msec
TPEP - PG after NALP
after NALOXONE
50 micro-volt

FIG.6.

Monkey II: There were no changes in the hypothalamic region or in the infundibulum. The stalk was destroyed by removal of the brain.

Monkey III: There was a great extent of damage in the hypothalamic region even the supra-optic nuclei showed a slight spongy state. The nuclei of the stalk neurones were neucrotic.

The adenohypophysis in the animals showed no lesions. There was no correlation between the histological findings and the extent of damage and the TPEP's results.

2.3 Discussion

TPEPs have been found to be of value in assessing cortical responses to acute experimental pain in various animals including the rhesus monkey.(13) Electrophysiologic and anatomic studies have demonstrated that the tooth pulp afferents consist exclusively out of A-delta and C-fibers.(14 15) These small diameter fibers transmit nociceptive impulses.

It has been shown that tooth pulp excitations, whether electrical, thermal, mechanical, or chemical, elecit sensations primarily, if not solely, characterized by pain. In view of its unique relationship to pain, tooth pulp stimulation via electrodes implanted into the dentine seems to represent a more effective and accurate method of producing acute experimental pain in man and animals than other techniques, including pinprick, ischemia of one limb, and intracutaneous, intra-arterial or intraperitoneal injection of drugs.

The pituitary region has so far not been considered as a neurologically active part of the brain. Registration of neural activity in the pituitary region suggests that this area is involved in more than hormonal production. Its integrated part in the neurophysiological pathways of the brain, however, is unclear and it is not known whether it is a mere relay station or it even plays a higher differentiated role in the overall brain function. Furthermore, TPEPs registration of the pituitary region has, so far as our knowledge is concerned, never been performed.

The TPEPs of the cortex in untreated normal monkeys were increased after injection of naloxone. The pituitary region shows characteristic TPEPs as well, but these remain the same, nearly unaffected by naloxone. After alcohol injection into the sella turcica, a severe decrease of the TPEPs of the cortex was observed as a sign for block of pain perception. Simultaneously, the TPEPs of the pituitary region, however, were increased, and even to more than double the height of control values. Naloxone showed a reversal effect, reappearance or increase of TPEPs in sensory cortex, versus reduction of TPEPs in the pituitary region.

Based on the contradictory response of the pituitary region as compared to the sensory cortex in TPEPs we assumed that the pituitary region might have an inhibitory action on the pain response in the sensory cortex.

The mechanisms leading to pain relief are varying: Pain relief is obtained immediately after NALP in some cases. This finding created the assumption that interruption of neuronal connection is the pain relief mechanism. In other cases, however, as repeatedly

reported at the recent World Congress of "Alcohol Adenolysis of the Pituitary Gland" in Verona (June 1981), pain relief is obtained after a period of a few days to two weeks following NALP. This finding led to the explanation that pain relief mechanism is not due to interruption of neuronal connections but is the consequence of interference with hormonal regulation. Furthermore, as reported at the same congress, complete pain control has also been observed in non-hormone dependent neoplastic disease. Permanent pain relief has been observed in some cases, in other cases reappearance of pain occurred following primary pain relief, after "NALP". Naloxone, a specific antagonist of endorphins at opiate receptors, sometimes led to reappearance of pain but could not always induce the reappearance of pain following relief after "NALP". The varying results seem not to depend on the techniques practised by the various investigators. Thus, the assumption might be drawn that varying pain relief mechanism of "NALP" might consist of several different factors.

Yanagida et al showed that even when a small part of the hypophysis was destroyed, pain relief could be achieved. Thus, pain relief following "NALP" does not seem to be related to the extent of damage caused to the gland. In this experiment it was also shown that even without damage of the adenohyphosis a decrease of the TPEP in PSC could be achieved suggesting that the gland is not involved in the mechanism of the immediate pain relief. The pathological findings in this experiment showed that the injected alcohol also can have his effects outside of the sella turcica as proved in one of the monkeys.

The term alcohol adenolysis of the pituitary region, as used in the literature, for the procedure of injecting alcohol into the sella turcica, therfore is misleading and should be changed.

Our present study suggests a mechnism which is capable of explaining the various conflicting results obtained by others which seem to oppose each other. TPEPs measured in the pituitary region, were facilitated with increase to even more than double the amplitude of the control values, while TPEPs in the sensory cortex disappeared. Our assumption is that hyperactivity (increase of TPEPs) after alcohol wounding (wounding effect) of the pituitary region or of a part of the hypothalamic area situated near to the PR is produced, and that this leads to a decrease of pain response in the sensory cortex (decrease of TPEPs). This wound effect may, to some degree, be influenced by endorphins, because naloxone, specific antagonist at opiate receptors reversed the opposed TPEPs responses in both places. Thus, in our thesis, inhibition through activation is the basis of pain relief after "NALP". This is exactly opposite to what has been assumed so far.

Our hypothesis of reactive activation of the pituitary region or of a part of the hypothalmic area by wounding also explains why, after reappearance of "NALP" induced pain, a second injection of alcohol produces pain relief again.

The hypotheses developed on the basis of our experimental results suggests that pain relief should be also obtained by other meams of activation of the pituitary region. Thus, electrical stimulation of the pituitary region has to have the same effect (chapter IV).

PART 2

CHAPTER III

Discussion, a new hypothesis for endogenous pain control

3.1 Introduction

Until ten years ago there were two opposing theories of pain perception: the first group of investigators thought that pain was the sensory effect of a stimulus to a receptor with its own control mechanism and specific peripheral apparatus, in contrast to this another group thought that 'the nerve impulses pattern for pain were produced by intense stimulation of non-specific receptors' (specific versus nonspecific receptor theory).(16)

In 1965, Melzack and Wall described and discussed their new hypothesis of a gate control system localised before the synaps with the first central transmission cells (T-cells) is reached and furthermore proposed:-

> '...that there exists in the nervous system a mechanism which we shall call the central control trigger that activates the particular selective brain processes that exert control over the sensory input.'

3.2 Endogenous pain modulating systems

The evidence for the existence of an endogenous control system in regulation of pain at the level of the central nervous system was the observation that electrical stimulation of certain brain-stem sites produces a kind of analgesia.(17, 18, 19)

It seems that the PAG (peri-aquaductal gray) plays an important role in this field of SPA (stimulation produced analgesia): especially stimulation of the ventrolateral part of the PAG is effective in producing profound analgesia.(20, 21, 22)

Also stimulation on higher levels of the brain, like the internal capsule, the septum and the caudate nucleus, even the cortex of the brain, can produce such kind of effect in the regulation of pain transmission.(23, 24)

At the same time, research was done on endogenous morphine like peptides and on endomorphins. It has been suggested that the OA (opiate analgesia) and the SPA (stimulation produced analgesia) operate by a common mechanism.(20)

It was seen that OA and SPA were most effective in the same area namely in the PAG, and that naloxone can produce a partial block of SPA.(25, 26)

Thereafter, it was suggested that opiates act by an inhibition of the pain transmitting system and that OA and SPA are associated with suppression of flexion relexes via the descending system.(20)

The group of Basbaum did much work to determine the interaction between the SPA and OA and the descending system to the spinal cord.(27)

3.3 Descending System

Basbaum et al found that a lesion of the dorsal part of the lateral funiculus markedly reduced the analgesia in the hindlimb ipsilateral and caudal to the lesion after stimulation of the PAG. A same kind of effect was observed after exogenous opioids in rats; however, bilateral lesions were much more effective in blocking OA.

A same effect of the DLF (dorsal lateral funiculus) lesions was described for analgesia from morphine, microinjected into the PAG. (28)

Radiographic studies showed a connection of the NRM (nucleus raphe magnus) by a compact bundle to the DLF at all spinal levels.

The NRM of the medulla is possibly the major source of spinal 5-HT, and stimulation of the area produces a profound analgesia. Basbaum suggests that the NRM is also involved in modulation of the descending system and especially in the view of noxious inputs.(28 29 30)

Ruda described efferent projections from the ventrolateral PAG to the NRM.(31) Basbaum suggested that stimulation of the PAG produces analgesia by a pathway in the DLF which is derived entirely from the NRM. However, naloxone blocks only partially the analgesia induced by stimulation of the PAG but it reverses completely the analgesia produced by NRM stimulation.(32) So it seems that a major part of the PAG induced analgesia must be mediated by other descending pathways which bypass the NRM and are not influenced by enkephalin.

The literature about the influence of serotonin in controlling pain shall be discussed separately.

Another important question is the role of the opioids in pain transmission. How do the opiates interact: at the level of the spinal cord inhibiting pain transmission neurons, or directly at brainstem level, or both? As early as 1964 Tsou described the observation that naloxone injected locally into the midbrain reverses the analgesia induced by systemic injection of morphine.(33) Direct spinal application of opiates, however, also produces analgesia.

3.4 Ascending System

Most theories of pain transmission suggest that the major spinal ascending system is located in the ventral half of the spinal cord (neo- and paleo-spinothalamic tract, as well as the spinoreticular fibers running medially into the reticular formation). However, there is evidence of the presence of multiple pain signalling pathways from the spinal cord to the lateral thalamus.

3.4.1 Dorsal column system

Primary and secondary afferent fibres are known ascending into the dorsal column nuclei (DCN) located in the caudal medulla. The fibres ascending in the dorsal columns (DC) had been viewed for many years only as carriers of tactile or propioceptive information.

Some of them, however, seem to be exclusively nociceptive, especially some of the secondary afferents - the dorsal column postsynaptic fibres (DCPS). 6.5% of this kind of fibres responded only to noxious mechanical stimuli.(34) They ascend ipsilateral in the DC and synaps mostly in the rostral and ventral part of the DCN.(35, 36, 37) The afferents of the DCN cross the midline in the lower brainstem and ascend in the medial lemniscus (ML) to the main somatosensory nuclei of the thalamus; the venteroposterolateral nucleus of thalamus (VPL): the medial part of medial geniculate body (MGm) and to the posterior thalamic complex (PO). (37, 38, 39)

3.4.2 Spino cervico thalamic system

The peculiar thing of this system is that it only exists in about 50% of the examined humans. Some investigators showed a response to a noxious mechanical and thermal stimulus in the neurons of this system and suggested a pain signalling function.(37, 40) 75% of the spinal cervical tract (SCT) axons ascend ipsilateral from the dorsolateral funiculus to the lateral cervial nucleus (LCN). The efferents of the LCN cross the midline in the caudal medulla and ascend in the ML to the VPL.(41) Some of the SCT fibres perhaps synapse directly into the lateral reticular nucleus and medullary cental gray.(42)

3.4.3 Neo-spinothalamic tract (n-STT)

Some of the fibers of this system have a response to an intense mechanical or thermal stimulation, suggesting a pain signalling system.(43)

The fibres cross the midline in the spinal cord and ascend in the ventrolateral spinal quadrant to the VPL without a synapse between the spinal cord and termination at brain levels. Terminations in other thalamic and subthalamic zones have been described.(37) A direct projection on to the cortex is uncertain but suggested.

3.4.4. Paleo spinothalamic tract (p-STT) and the spinoreticular tract (SRT)

These systems ascend also in the ventrolateral spinal quadrant. The p-STT cross the midline in the spinal cord and some of them may be homolateral of course.(44) The fibres projecting directly from spinal cord to the intralaminar thalamic nuclei are few in number.(45) Other fibres connect to the reticular formation (RF). The spinal input to the RF is diffuse, multi-synaptic, and overlaps with other non-spinal RF-connections (the spinoreticular tract).(16 17) The ascending pathway of the SRT may be bilateral instead of ipsilateral as mostly suggested.

In contrast to the n-STT the velocity of impulses in the p-STT and the SRT seems to be much slower.(37 47) A different anatomical structure (the fibres of the p-STT and SRT run more medially than the DC, SCT, and n-STT) as well as a difference in velocity suggest a separate involvement in pain transmission.

3.5 The role of internal opiates and opiate receptors

'Among the remedies which it has pleased Almighty God to give man to relieve his sufferings, none is so universal and so efficacious as opium.'

T. Sydenham 1680

As early as 1967, the possibility that 'opioids mimic a naturally ongoing process' has been discussed (48, 49) because all opioids produce their highly selective effects at very low concentrations. The basic similarities in their molecular architecture suggest the possible interaction of opiates with a geometrically and chemically complementary receptor site. The possibility to transform opiate agonists into antagonists by very slightly molecular modifications supports the receptor concept.(50) The potency of opiate agonists to inhibit rhythmic contractions of the guinea pig ileum smooth muscle, induced by an electric stimulator made it possible to measure receptor affinity for opioids.

Electric stimulation of a plexus causes release of acetylcholine from the postganglionic cholinergic neurons. This release can be diminished by opiates causing an inhibition of the twitch amplitude which is blocked and reversed by the opiate antagonist. Other substances can produce the same effect, however, without the possibility of a reversal by these antagonists.(51) So it was found that receptor affinity and pharmacological potency correlated remarkedly well for both opiate-antagonists and agonists.(50)

The observation in vitro experiments that sodium can increase the enhancement of opiate antagonists and decrease the binding of agonists made it possible to evaluate a wide range of opiates.(54)

The sodium index predicts the extent to which an opiate is agonistic or antagonistic.

Measurement of the binding of radioactive drugs to brain tissue made it possible to demonstrate specific opiate receptor bindings in the brain.(52, 53, 54) A radioactively marked opioid is injected and after a short interval the nonspecifically bound substances are washed out again. This binding affinity is closely related to the affinity to guinea-pig intestine which compared with the pharmacological potency.(50) The existence of specific opiate receptor sites in vertebrates indicated the presence of a natural morphine-like substance.

In 1974 the first reports were published claiming the identification of opiate-like peptides in brain areas which have been named (55, 56, 57) Met5-enkephalin and Leu5-enkephalin. They noted that Met5-enkephalin occurred at position 61-65 of beta -lipotropin (beta-LPH) a peptide isolated from pituitary gland so far only known to play a role in the fat metabolism.

Teschmacher and Cox reported in 1975 opiate-like material isolated in the hypophysis. This material occurred (the important one) at position 61-69 of beta- LPH.(58, 59) One of the most important questions was the role of the endogenous opiate-like peptides and the role of the opioid receptor sites. The guinea pig ileum experiments suggest an interaction with a neurotransmitter system. Other experiments showed 'largely confined' receptor binding of synaptosome fraction of homogenized brain tissue to opiate receptors, indicating a role in the neuro-transmitter system.(50)

Nowadays, it is suggested that the enkephalin acts as an inhibitory neuro-transmitter especially in neuronal systems that mediate the integration of sensory information having to do with pain and emotional behaviour.

Snyder suggested that partial depolarization of the excitatory neuron occurs by induced release of enkephalin from an enkephalinergic neuron. The enkephalin then binds to opiate receptors on the terminal of the excitatory neuron. It is well-known that the amount of the neurotransmitter release is triggered proportional to the degree of depolarization. Enkephalin released at terminals bound to the opiate receptors increased the conductance of sodium across the membrane and partially depolarises it. Thus, a nerve impulse triggers a decrease of the amount of the excitatory transmitter release.(50) In contrast to Snyder, other investigators suggested that the opiates may act by impairing the sodium influx triggered at the postsynaptic membrane by excitatory neurotransmitters.(60, 61, 62) The question whether there exists presynaptic inhibition or post-synaptic inhibition is however academical because the outcome is the same.

3.6 The role of serotonine (5-HT):

In order to investigate the effects of 5-HT many tools exist to manipulate the serotonergic transmission such as:

1. modification of synthesis
2. inhibition of the storage
3. stimulation of the release
4. inhibition of re-uptake
5. the use of receptor agonists or antagonists
6. the use of specific neurotoxins.

For the study of the influence of 5-HT, there are other techniques available such as producing lesions in the area of the nucleus raphe medianus and magnus and in the dorsallateral funiculus. Electrophysiological investigations in the same areas have been performed. The influence of tryptophan deficient diet on the 5-HT level is well-known.

Most such studies showed changes in behavioural responses to noxious stimuli compared to normal untreated animals. It is often difficult to distinguish between sensitivity and reactivity to painful stimuli. It may be that the alterations in the responses to noxious stimuli observed in animals with a change in serotonin concentrations are produced by changes in reactivity rather than changes in sensitivity. This implies that 5-HT manipulation alters motor responses.(63)

As early as 1965, histochemical studies showed 5-HT terminals in the lateral, the dorsal and especially in the ventral horn. It was suggested that the 5-HT terminals (e.g. the noradrenergic terminals) are directly contacted with the alpha -motorneurons and with the autonomic nerve cells in the sympathetic lateral column.(64) Another point of interest is the observation that besides descending pathways from the NRM, the more rostrally

located raphe nuclei (NR medianus and NR dorsalis) send axons into the medial forebrain bundle with large numbers of terminal collaterals in diencephalic and telencephalic brain regions, including the hypothalamus with a high density of endings in the nucleus arcuatus. (65, 66)

Different lesions aimed at the cell bodies, axons or terminals of serotonergic neurons seem to produce neurochemical damage in the forebrain while lesions of only axons and terminals lesions resulted in hyperalgesia. Hypothetically these pathways should interfere with other systems in the hindbrain tissue like the central gray.(67)

Autoradiographic investigations with 3H-labelled 5-HT in the nerve cell bodies showed in the hypothalamic area short tracks which may be consistent with a neuroregulatory role in the interneural transmission.(68) Even a connection between the nuclei raphe and the pituitary gland may be a possibility. Stimulation of the more rostral raphe nuclei attenuate the LH-release.(69)

3.7 An hypothesis concerning the role of the pituitary region (PR) in the endogenous pain control mechanism

Our experiments in the monkeys, as described in Chapter 2, showed, after tooth pulp stimulation, an opposite effect in the response of the PR and the PSC suggesting an inhibitory function of the PR in the endogenous pain transmission as is already known for the PAG (ch 3.2).

In our thesis, interactions between the PR and the PAG are supposed. This thesis supports the findings that in the rat the

discrete electrolytic lesions in different parts of the medial hypothalamus induce clear cut hyperanalgesia.(70) Not only an alteration of the endorphins, but also an interaction with sensory pathways, must be one of the possibilities to explain the data found in these experiments. However, the actual process of integration of the PR with the PAG is unclear.

In our thesis the neuroactivity of the PR is induced by ascending pathways, like the SRT and p-STT (ch 3.4.4), from the spinal level to the PR and perhaps mediated by the NR system (ch 3.6). It is likely to assume a self control system of the neuroactivity of the hypophyseal area by a feedback mechanism which induces a balanced control of the endogenous pain transmission to the PSC similar to other functions of the central nervous system. In our simplified model of the role of the PR in the pain control mechanism (fig 7), the opiates act by decreasing the amount of the excitatory transmitter release in the way of neuromodulation (ch 3.5), by enkephalinergic short neurones which have been described especially in the medial hypothalamus.(71)

Thus the following assumptions can be made:

1. naloxone decreases the TPEP in the PR and increases the TPEP in the PSC - experiment II.
2. exogenous opiates (like fentanyl) increase the TPEP in the PR and decrease the TPEP in the PSC - experiment III.
3. stimulation of the PR induces a decrease of the TPEP in the PSC which can be reversed only partially by naloxone experiment IV.

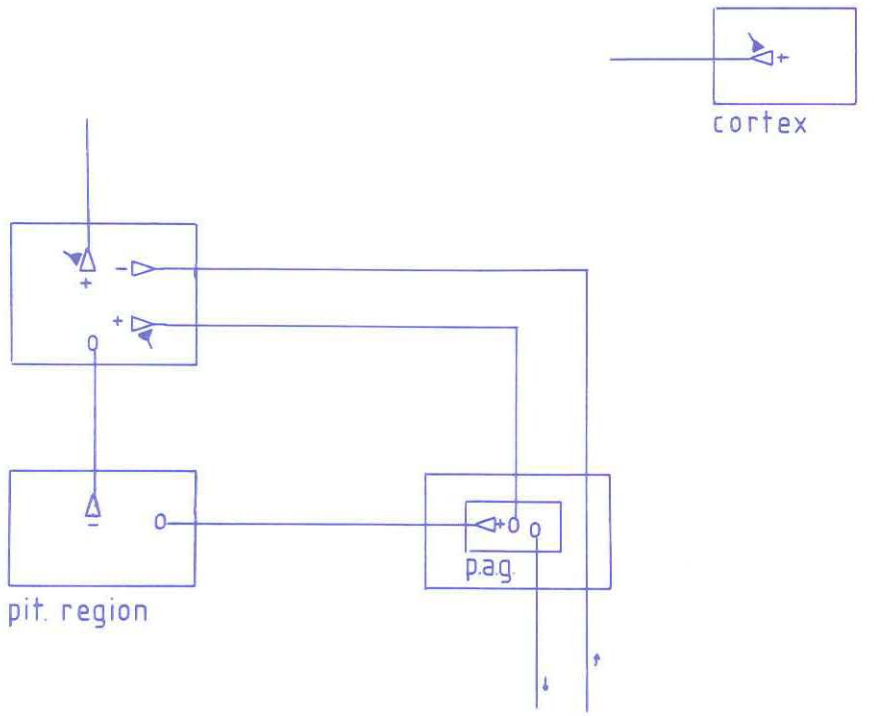


FIG. 7: HYPOTHETICAL SIMPLIFIED MODEL OF THE ROLE OF THE P.R. IN THE PAIN CONTROL MECHANISM

p.a.g. = peri-aquaductal gray

\+ = excitation

\- = inhibition

◄ = neuromodulation (enkephalinergic)

↑ = ascending pathways

↓ = descending pathways

CHAPTER IV

Experimental Work

4.1 Experiment 2: The influence of naloxone on the tooth pulp evoked potential (TPEP) of the pituitary region (PR) and of the primary somatosensory cortex (PSC) in the rabbit.

4.1.1 Materials and Methods

Seven male adult north sealand white rabbits, weighing 2.5 to 3 kg served as subjects.

Under hypnorm (fluanison and fentanyl) anaesthesia, two silver bone screws were placed on the PSC and two other bone screws were placed in the midline of the frontal skull. A 16 gauge epidural stainless-steel needle containing a wire electrode with a hook at its tip was advanced through the right nostril into close proximity of the nasal septum. Progression of the needle was carefully monitored by bi-plane fluoroscopy until the needle tip had reached its final position. The wire electrode was kept in this position with a hook engaged in the PR, after which, the needle was gently withdrawn. The wire was passed subcutaneously to the top of the skull. To induce the pain stimulus, small holes were drilled through the enamel and dentine of both maxillary incisors to a depth of about 0.5 mm through which two self-threading pins were

placed and embedded into the tooth pulp. The pins were soldered to insulated connecting wires which were placed subcutaneously to the front of the skull. The exposed junctions of the dental pins and steel wires were insulated from the oral cavity by self-curing dental acrylic.

All bone screws and wire electrodes were secured to the skull with dental acrylic (pict. 1). Following the implantation of the electrodes the rabbits were allowed to recover for at least 48 hours.

TPEP recording sessions were conducted with the unsedated rabbit placed in a restraining box in the upright position. Stimuli and evoked potential responses were recorded from PSC and PG employing a Grass polygraph recorder equipped with an A-C amplifier. A Hewlett-Packard storage oscilloscope was used for continuous monitoring.

Square waves were generated by an electrical stimulator (Grass S-20) equipped with modified stimulus isolation unit and constant current. Analysis times were 100 and 300 msec. The responses to 45 consecutive stimuli administered to each animal were averaged employing a Hewlett-Packard clinical averager (fig. 8). Amplitudes were measured from the base to the peak of each component wave. The electrical stimuli consisting of monophasic square waves of 0.3 msec duration and 10 volts were delivered at 3.0 second intervals across the pulp cavity.

After TPEP recordings in the untreated animals had been completed, naloxone at a dose of 0.05 mg/kg was administered intravenously and subsequently the measurement of the TPEP of the PR was repeated. After at least 4 hours a new dose of naloxone was admin-

istered as previously described, and subsequently, after 10 minutes, the measurement of the TPEP of the PSC was repeated.

After measurements had been completed, the rabbits were anaesthetised and the brain removed. This was to ensure the electrodes were well positioned (pict. 2).

4.1.2 Results

The animals withstood all phases of the experiment well, and there was no indication of behavioural or physiologic changes. In particular, purposeful body movements, as well as rejection behaviour, anger, and appetite remained unchanged.

4.1.2.1 EEG results (fig. 9)

Before tooth pulp stimulation, the normal EEG was recorded. In the cortex a normal EEG was monitored, which means a non excited, very settled animal in an awake state was present. The PR activity showed high voltage slow activity. After injection of naloxone there was only a change in PR activity with a slowing of the EEG pattern and an increase of the voltage.

4.1.2.2 TPEPs of the PSC

The electrical stimulus to the tooth pulp produced a characteristic triphasic response. In the animals the tracing showed an initial steep negative deflection of the potential followed by two positive delections. The amplitude of the second positive wave

PICTURE 1 : THE BONE SCREWS AND WIRE ELECTRODES SECURED TO THE FRONT OF THE SKULL.

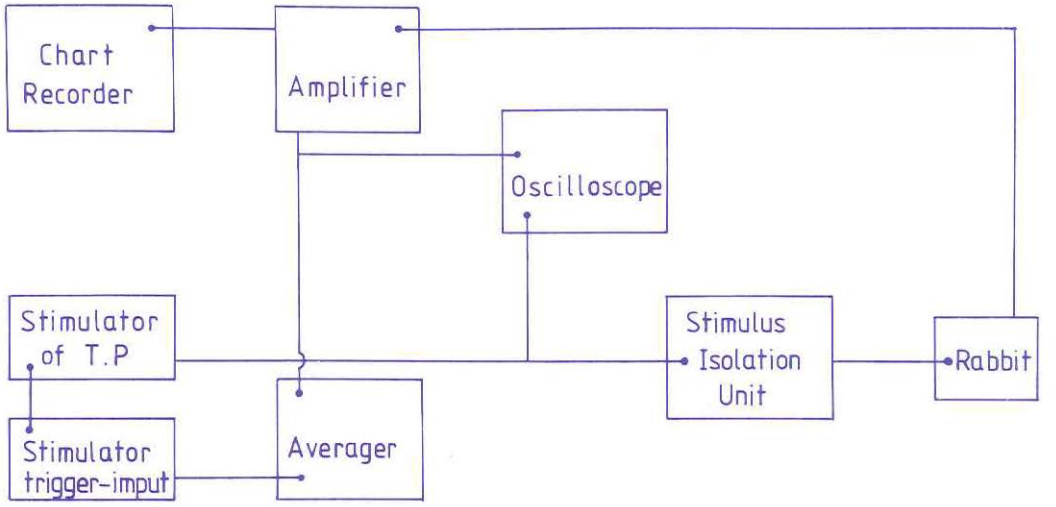
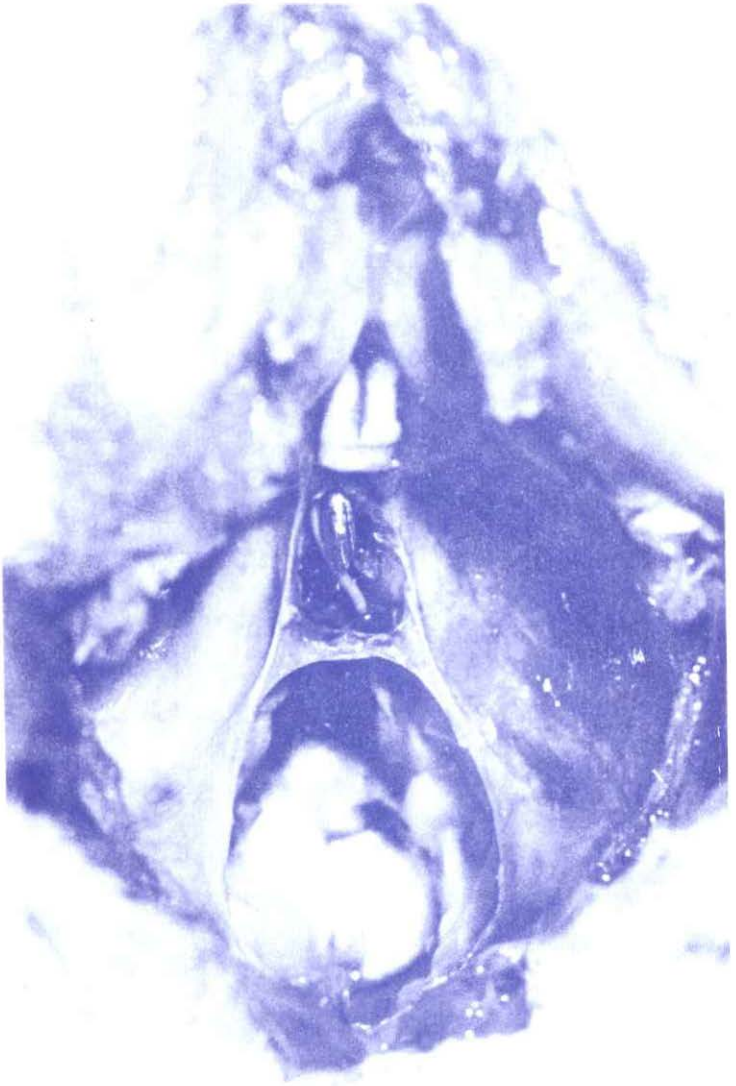


FIG. 8: SCHEMATIC OF THE EXPERIMENTAL SET UP (exp. 3 and 4).



PICTURE 2 : THE POSITION OF THE NEEDLE AND WIRE ELECTRODE IN THE SERRA TURCICA.

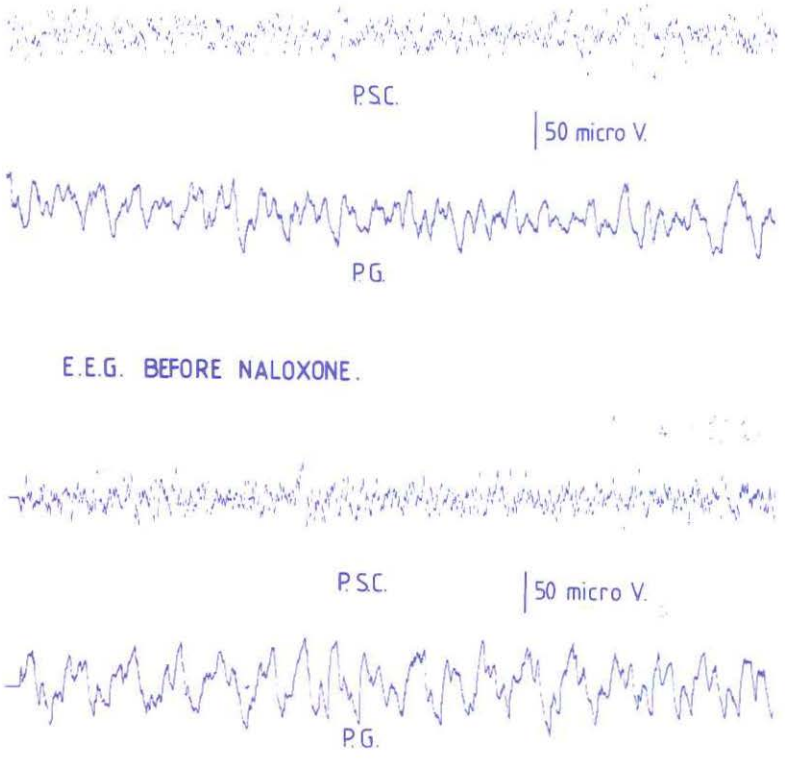


FIG. 9: THE INFLUENCE OF NALOXONE ON THE E.E.G. OF THE PRIMARY SOMATOSENSORY CORTEX (P.S.C.) AND OF THE PITUITARY REGION (P.R.)

appearing approximately 30 msec after the presentation of the stimulus seemed to respond with the intensity of the stimulation. The averaged amplitude was 18.7 microV. After injection of naloxone, the second positive wave increased significantly in amplitude in all animals with, overall, about 35% (fig. 10) to mean voltage of 25.3 microV.

4.1.2.3 TPEPs of the PR

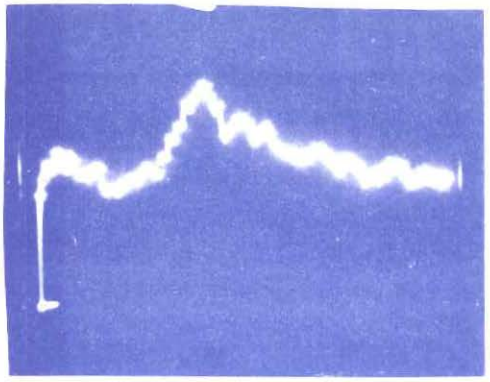
Electrical stimulus of the tooth pulp produced a polyphasic response. The amplitude of the second positive wave appearing approximately 20 msec after the presentation of the stimulus seemed to reflect the intensity of the stimulation. The averaged amplitude was 30.5 microV. After injection of naloxone the second positive wave decreased significantly in amplitude in all animals with, overall, about 36% (fig. 11) to 19.2 microV.; this is in contrary to the response of the PSC where the original response increased after injection of naloxone.

4.2 Experiment 3: The influence of an exogenous opiate (fentanyl) on the TPEP of the pituitary region (PR) and of the primary somato sensory cortex (PSC) in the rabbit.

4.2.1 Materials and Methods

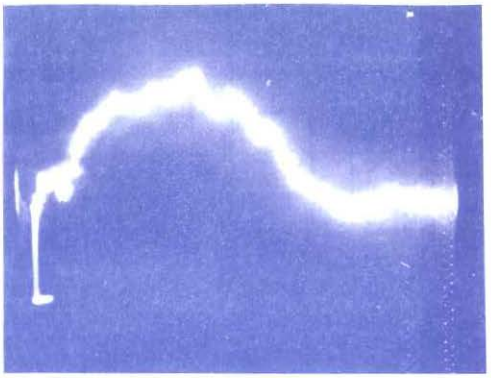
Six male adult north sealand white rabbits weighing 2.5 to 3 kg served as subjects. Under hypnorm (fluanison and fentanyl) anesthesia all electrodes were placed and secured to the skull in

A



100 MSEC.

B



100 MSEC.

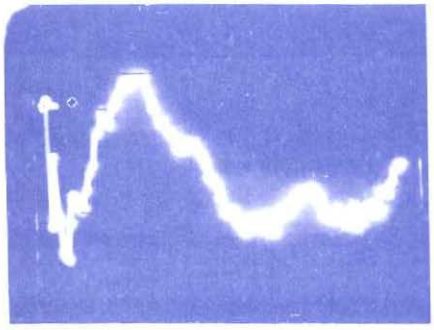
The influence of naloxone on the T.P.E.P. of the P.S.C.

A: before naloxone.

B: after naloxone.

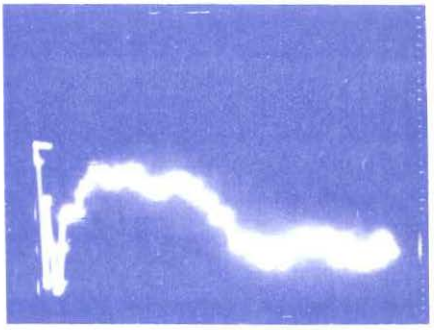
FIG. 10

A



300 MSEC.

B



300 MSEC.

The influence of naloxone on the T.P.E.P. of the P.G.

A: before naloxone.

B: after naloxone.

FIG. 11

the same way as described in experiment 2, (ch 4.1.1). Following the implantation of the electrodes, the rabbits were allowed to recover for at least 48 hours. TPEP recording sessions were conducted as previously described in experiment 2 (ch 4.1.1).

After the TPEP recordings in the untreated animals had been completed, fentanyl at a dose of 0.01 mg/kg was administered intramuscularly and subsequently the measurements of the TPEP of the PR was repeated. After at least 4 hours a new dose of fentanyl was administered as previously described and subsequently after 10 minutes the measurement of the TPEP of the PSC was repeated.

After all measurements had been completed, the rabbits were anesthetised and the brain removed. This was to ensure the electrodes were well positioned.

4.2.2 Results

The animals withstood all phases of the experiment well and there was no indication of behavioural or physiological changes. In particular, purposeful body movements, as well as rejection behaviour, anger, and appetite remained unchanged.

4.2.2.1 EEG results (fig. 12)

Before tooth pulp stimulation the normal EEG was recorded. In the cortex a normal EEG was monitored, which means a non-excited, very settled animal in an awake state was present. The PR activity showed high voltage, slow activity. After injection of fentanyl there was only a change in PR activity with an acceleration of the EEG pattern and a decrease of the voltage.

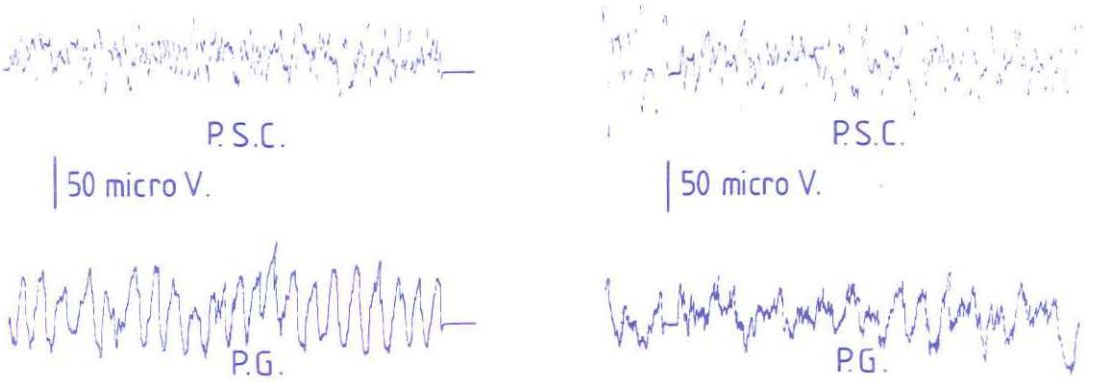


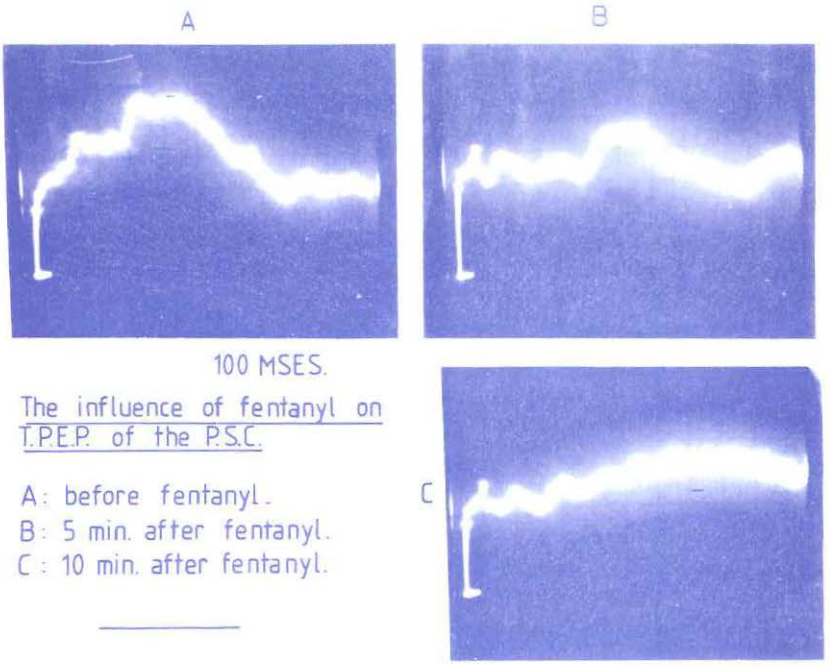
FIG. 12: THE INFLUENCE OF FENTANYL ON THE E.E.G. OF THE PRIMARY SOMATOSENSORY CORTEX AND ON THE E.E.G. OF THE PITUITARY REGION.

4.2.2.2 TPEPs of the PSC

The electrical stimulus to the tooth pulp produced a characteristic triphasic response. In the animals the tracing showed an initial steep negative deflection of the potential, followed by two positive deflections. The amplitude of the second positive wave appearing approximately 30 msec after the presentation of the stimulus seemed to respond with the intensity of the stimulation. The averaged amplitude was 21 microV. After injection of fentanyl, the second positive wave decreased in all animals significantly in amplitude with, overall, about 24% to an averaged voltage of 16 microV. (fig. 13)

4.2.2.3 TPEPS of the PR

The electrical stimulus to the tooth pulp produced a polyphasic response. The amplitude of the second positive wave appearing approximately 20 msec after the presentation of the stimulus seemed to reflect the intensity of the stimulation. The averaged amplitude was 27 microV. After injection of fentanyl, the second positive wave increased significantly in amplitude in all animals with, overall, about 24% to 33.5 microV. (fig. 14); this was in contrary to the response of the PSC where the original response decreased after injection of fentanyl.

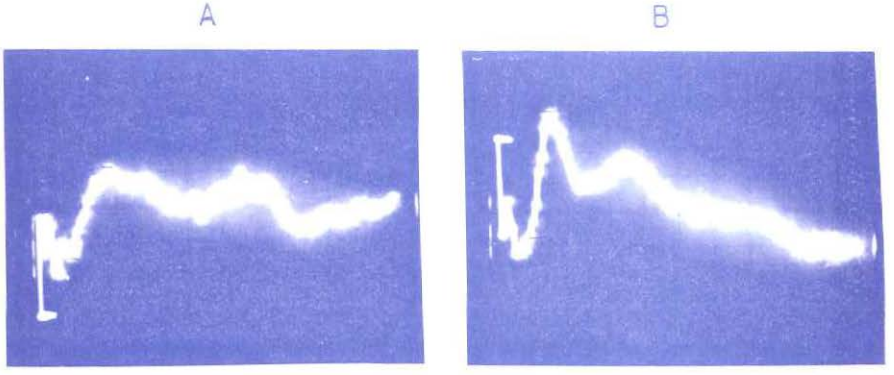


100 MSES.

The influence of fentanyl on T.P.E.P. of the P.S.C.

A: before fentanyl.
B: 5 min. after fentanyl.
C: 10 min. after fentanyl.

FIG. 13 .



300 MSEC. 300 MSEC.

The influence of fentanyl on the T.P.E.P. of the P.G.

A: before fentanyl.
B: after fentanyl.

FIG. 14 .

4.3 Experiment 4: The influence of stimulation of the pituitary region (PR) on the TPEPs of the primary somatosensory cortex (PSC)

4.3.1. Materials and Methods

Six male adult north sealand white rabbits weighing 2.5 to 3 kg served as subjects. Under hypnorm (fluanison and fentanyl) anaesthesia all electrodes were placed and secured to the skull in the same way as in experiment 2 (ch 4.1.1). The only difference was the implantation of a second wire electrode close to the first into the PR.

Bipolar stimulation of the PR was generated by an electrical stimulator (Philips P.M. 5162 Sweep generator) equipped with a stimulus isolation unit. (fig. 15) After control measurements of the TPEP of the PSC, stimulation was started and continued for 10 minutes using a voltage of 3 V and a frequency of 10Kc. The measured intensity was 0.8 mA. TPEPs of the PSC were recorded immediately after finishing stimulation. TPEP recording of the PSC was repeated one hour after stimulation of the PR and another hour later a new session of stimulation and TPEP recording was started.

After 24 hours the TPEP of the PSC was measured before and after stimulation. PR stimulation was compared with an intravenous injection of 0.05 mg/kg naloxone.

TPEP recording sessions were conducted as previously discussed in experiment 2 (ch 4.1.1).

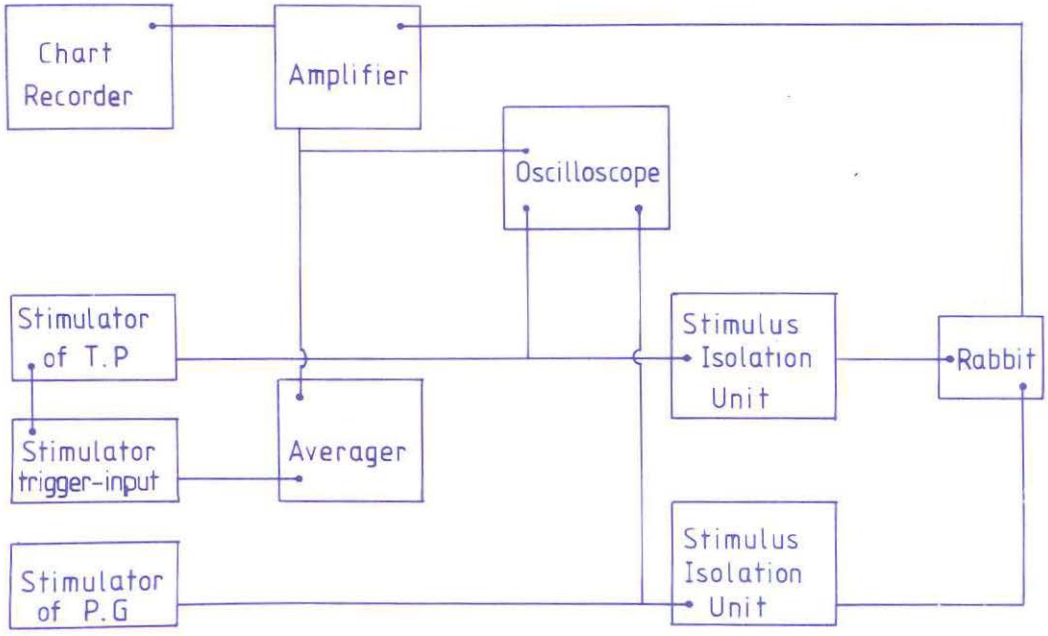


FIG. 15: SCHEMATIC OF THE EXPERIMENTAL SET UP. (exp. 4).

4.3.2. Results

The animals withstood all phases of the experiment well and there was no indication of behavioural or physiologic changes. In particular, purposeful body movements as well as rejection behaviour, anger, and appetite remained unchanged; also during the stimulation of the PR.

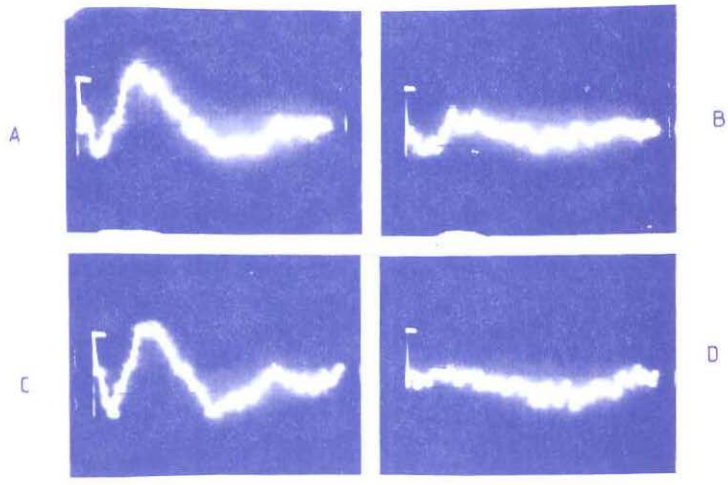
4.3.2.1 TPEPs of the PSC

The electrical stimulus to the tooth pulp produced a characteristic triphasic response. In the animals the tracing showed an initial steep negative deflection of the potential, followed by two positive deflections. The amplitude of the second positive wave appearing approximately 30 msec after the presentation of the stimulus seemed to respond with the intensity of the stimulation. The averaged amplitude was 25 microV. After the actual stimulation of the PR the second positive wave decreased significantly in amplitude in all animals with, overall, about 34% to averaged amplitude of 16.5 microV. One hour after the actual stimulation of the PR, the TPEP of the PSC had the same amplitude as the control values measured before stimulation. After a second stimulation period of 10 minutes the amplitude decreased much more than after the first stimulation with, overall, about 48% to an averaged value of 12.9 microV. (fig. 16)

PR stimulation combined with an intravenous injection of naloxone produced a decrease of the TPEP amplitude with, overall, 26%. This is 23% less effect than after stimulation of the PR with injection of naloxone.

The best results were found when the electrodes were touching just the stalk. Two animals showed another effect. After stimulation there was an increase of the TPEP response with about 40%. By the examination of the position of the electrodes it was shown that in these two animals the electrodes had penetrated the floor of the sella turcica and were touching the surface of the brain just caudal of the recessus infundibularis.

Therefore they were excluded from this experiment.



The effect of stimulation of the pit. reg. on the T.P.E.P. of the P.S.C.

A : before stimulation.
B : after stimulation.
C : 1h. after stimulation.
D : after the second stimulation period.

FIG. 16 .

CHAPTER 5

General Discussion and Conclusions

In the past, the pituitary region (PR), had not been considered a neurological part of the brain but merely as a hormone regulating area. However, with its well documented hormonal connections to the hypothalamic system, with its own interconnections with the visible structures and its long processes distributed through the brain, and especially in the view of interactions into the periventricular gray matter, it is difficult to accept that the PR, with its surrounding structures, is merely a relay station and does not play a higher differentiated role in the overall brain function.

The existence of a high level of beta-endorphins and enkephalin in the PR suggest an important role of this area in pain.(72) However, the relations between the pituitary endorphin and analgesia are still very controversial.

To our knowledge, tooth pulp-evoked potentials have not been recorded from the pituitary region of experimental animals until now. Therefore, it is a totally new finding that the injection of alcohol into the sella turcica in the monkey had a totally opposite effect on the tooth pulp evoked potentials (TPEPs) of the PR, and of the primary somatosensory cortex (PSC), suggesting an inhibitory mechanism of the PR upon the pain response in the sensory cortex. (exp. 1)

The effect of naloxone on the TPEP of the PSC and the PR also proved opposite (exp. 2). The same result was found after injection of an exogenous opiate like fentanyl (exp. 3).

The electrostimulation of the PR induced a decrease of the TPEP of the PSC suggesting the same result as NALP (exp. 4). Another interesting finding in this experiment was that when the electrodes were not well positioned there were signs of increased TPEP response in the PSC instead of a decrease as shown in the other animals. The best results were obtained when the electrodes were touching just the stalk. This suggests that the stalk plays the most important role in this field. An influence of it on other parts of the brain as the hypothalamic area, however, cannot be excluded, and can be a possibility to explain the datas. An influence of the electro- stimulation on the endorphins by direct stimulation of this system with an overproduction can also be proposed.

In our study, however, it was impossible to reverse totally the effect of electrostimulation of the PR by naloxone. The decrease of the TPEP of the PSC after naloxone was less, probably because this decrease was also partially influenced by the effect of naloxone in other parts of the brain. Thus, the interference with central sensory pathways must be one of the key factors to explain our datas.

In our thesis, there must be interactions between the PR and the peri-ventricular and/or periaquaductal gray. The PR acts in this way as an inhibitory area in pain transmission through the descending inhibitory pathways. In which way the sensory pathways originating in the PR run through the central nervous system is still unclear, and it is not easily understood because of the

multiplicity of interconnections and pathways through the medial hypothalamus (MH) and because of the exceptionally high number of alleged mediators or neuromodulators present in this area.(68)

Our data and the analgesic effects following electrical stimulation of the medial hypothalamus,(73) and the induced hyperalgesia by discrete lesions of parts of this area,(72) suggest strongly a connection between the PR, the medial hypothalamus, and the endogenous pain control mechanism.

The interference of opiates and opiate antagonists in this system, as shown in experiments 2 and 3, can act in the way of neuromodulation, as discussed in chapter 3.5, or can be understood as an interference with real neurotransmission via enkephalinergic neurons involved as a part of the sensory pathways.

In our thesis, the neuroactivity of the PR is induced by ascending pathways which fibers are running medially in the reticular formation and are perhaps mediated by the raphe nuclei (ch. 3.4.4 and ch. 3.6).

In conclusion, the objectives formulated in chapter 1.4 and chapter 3.7 of this thesis seem to have accomplished:

1. Injection of alcohol into the sella turcica in the monkey decreases the Tooth Pulp Evoked Potential (TPEP) of the Primary Sensory Cortex (PSC) and increases the TPEP measured in the Pituitary Region (PR) suggesting an inhibitory effect of the PR upon the pain response in the sensory cortex.

2. Naloxone injected into the monkey before the injection of alcohol into the sella turcica, induces an increase of the TPEP of the PSC and induces an decrease of the TPEP measured in the PR. The same opposite effect of naloxone was observed after the injection of alcohol into the sella turcica.
3. In the rabbit naloxone decreases the TPEP measured in the PR, and increases the TPEP of the PSC.
4. In the rabbit an exogenous opiate like fentanyl increases the TPEP measured in the PR and decreases the TPEP of the PSC.
5. Stimulation of the PR induces a decrease of the TPEP of the PSC which can be reversed only partially by naloxone.

GENERAL CONCLUSION

1. The pituitary region and/or a part of the hypothalamic area situated near to the pituitary region plays an important role in the endogenous pain control mechanism.

2. The term neuroadenolysis of the pituitary gland (NALP) as used in the literature, for the procedure of injecting alcohol into the sella turcica, is misleading and should be changed.

List of Abbreviations Used

DC	Dorsal Columns
DCN	Dorsal Column Nuclei
DCPS	Dorsal Column Postsynaptic Fibers
DLF	Dorsal Lateral Funiculus
FSH	Follicle Stimulating Hormone
GH	Growth Hormone
5-HT	Serotonine
17-KS	17 Keto Steroids
LCN	Lateral Cervical Nucleus
LH	Luteinizing Hormone
β-LPH	Beta-Lipotropin Hormone
MGm	Medial Part of Medial Geniculate Body
MH	Medial Hypothalamus
ML	Medial Lemniscus
MRF	Mescencephalic Reticular Formation
NALP	Neuroadenolysis Of The Pituitary Gland
NRM	Nucleus Raphe Magnus
n-STT	Neo Spinothalamic Tract
OA	Opiate Analgesia
PAG	Periaquaductal Gray
PO	Posterior Thalamic Complex
PR	Pituitary Region
PSC	Primary Somatosensory Cortex
p-STT	Paleo Spinothalamic Tract
RF	Reticular Formation
SC	Sensory Cortex
SCT	Spino Cervical Tract
SPA	Stimulation Produced Analgesia
SRT	Spino-reticular Tract
VPL	Ventro Posterolateral Nucleus of Thalamus

SAMENVATTING

De factoren betrokken bij het verlichten van onduldbare pijn bij patienten met een maligniteit, door de methode zoals in de literatuur genoemd "neuro-adenolysis van de hypophyse", waren in nog onvoldoende mate bekend. Een interactie met de hormonale regulatie, overproduktie van endorphines geinduceerd door de injektie van absoluut alcohol in de sella turcica en een placebo effekt worden als eventuele verklaringen gegeven. De opzet van de beschreven studies was de mogelijke rol van de hypophyse streek (PR) in de sensibele banen van het centrale zenuwstelsel als onderdeel van een endogeen pijnregulatie-mechanisme te onderzoeken.

Hoofdstuk 1 geeft een overzicht van de literatuur betreffende de "neuro-adenolyse van de hypophyse", terwijl hoofdstuk 2 handelt over de methoden en resultaten van de experimenten bij apen. Elektrische potentialen in de sensibele cortex (PSC) en in de hypophysestreek (PR) bij rhesus-apen na stimulatie van de tandpulpa (TPEP) werden voor en na de injectie van alcohol in de sella turcica geregistreerd. In hetzelfde experiment werd het effekt van naloxone op de TPEPs voor en na deze injectie onderzocht. TPEPs waargenomen in de PSC werden duidelijk geinhibeerd door de alcohol injectie terwijl de respons in de PR hierdoor werd vergroot. Deze waarnemingen suggereren een inhiberende rol van de PR bij de pijnperceptie.

Tevens maken de pathaloog-anatomische bevindingen in dit experiment het waarschijnlijk dat de adenohypophyse zelf niet is betrokken bij het ommiddelijk optreden van pijnverlichting na injectie van alcohol in de sella turcica. De term neuroadenolyse van de hypophyse is daarom misleidend en dient veranderd te worden.

In Hoofdstuk 3 worden sommige mechanismen die betrokken zijn bij de neurotransmissie van de pijnprikkels en een hypothese die betrekking heeft op de rol van de hypophysestreek in het endogene pijnregulatie-systeem beschreven.

In Hoodfstuk 4 worden de methoden en resultaten van 3 experimenten bij konijnen vermeld. Allereerst werd de invloed van naloxone op de TPEP in de PSC en in de PR nagegaan terwijl in experiment 3 het effekt van een exogeen opiaat werd onderzocht. De invloed van elektrostimulatie van de PR op de TPEP in de PSC werd in experiment 4 bepaald. Naloxone verhoogt de amplitude van de TPEP in de PSC en vermindert de respons in de PR. Het effekt van een exogeen opiaat op de TPEP in de PSC was eveneens tegenovergesteld aan de respons in de PR. Een vermindering van de amplitude in de PSC en een toename van de respons in de PR werd waargenomen. Elektrostimulatie van de PR veroorzaakte een inhibitie van de TPEP in de PSC, wat geinterpreteerd kan worden als een inhibitie van de pijnperceptie terwijl deze uitkomst slechts voor een klein gedeelte door naloxone kon worden beinvloed.

De algemene discussie en de conclusies betreffende de rol van de PR in het endogene pijnregulatie-mechanisme worden beschreven in hoofdstuk 5.

SUMMARY

The mechanism by which instant relief of pain, due to advanced cancer, is obtained subsequent to the so-called "neuroadenolysis of the pituitary region (NALP)" was still poorly understood. Interference with hormonal regulation, overproduction of endorphins activated by the injection of alcohol into the sella turcica and placebo effect have been suggested as possible factors.

The purpose of the present studies was to determine the possible role of the pituitary region in central sensory pathways as a part of the endogenous pain control mechanism.

In Chapter 1, the survey of the literature concerning "NALP" has been described, while Chapter 2 discusses methods and results of the monkey experiments. Tooth pulp-evoked potentials (TPEPs) recorded from the primary somato sensory cortex (PSC) and from the pituitary region (PR) of the rhesus monkeys were recorded before and after an injection of alcohol into the sella turcica. Subsequently, the effect of the opiate antagonist naloxone on the TPEPs was investigated before and after the injection of alcohol. TPEPs recorded from the PSC showed marked inhibition following this application of alcohol while the TPEPs recorded from the PR were facilitated, suggesting an inhibitory action of the PR on the pain perception.

Furthermore, the pathological findings in the monkeys suggest that the adenohypophysis is not involved in the mechanism of the immediate pain relief. Therefore, the term "neuroadenolysis of the pituitary gland" should be changed.

In Chapter 3, some of the mechanisms involved in pain transmission and the hypothesis concerning the role of the pituitary region in the endogenous pain control system have been discussed.

Chapter 4 is concerned with the description of three different experimental procedures in rabbits. At first, the influence of naloxone on the TPEP of the PR and of the PSC has been recorded, while in experiment 3 the effect of an exogenous opiate on the TPEP of the PR and of the PSC had been identified. The effect of electrical stimulation of the PR on the TPEPs of the PSC has been investigated in experiment 4. Naloxone increased the amplitude of the TPEP of the PSC and decreased the response in the PR. The effect of an exogenous opiate of the TPEP on the PSC and the PR are also proved opposite, a decrease of the amplitude of the TPEP of the PSC and an increase of the TPEP of the PR was recorded. Stimulation of the PR induced an inhibition of the TPEPs of the PSC, understood as inhibition of pain perception through activation of the PR or his surrounding structures. This could only be partially blocked by naloxone.

The general discussion and conclusions concerning the important role of the PR in the endogenous pain control mechanism has been described in Chapter 5.

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CURRICULUM VITAE.

De schrijver van dit proefschrift werd in 1949 te Monster geboren en bezocht achtereenvolgens de H.B.S. te Waalwijk, het Chr. Lyceum te Dordrecht en de Rijks H.B.S. te Oud-Beyerland. In 1968 werd het eindexamen H.B.S.-B met goed gevolg afgelegd. In datzelfde jaar begon hij met zijn medicijnenstudie aan de Medische Faculteit te Rotterdam. In 1973 werd aan de Erasmus Universiteit het doctoraal examen met succes afgelegd, waarna in october 1974 de bevordering tot arts plaatsvond.
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De opleiding werd voltooid op 1 januari 1982, waarna hij werkzaam was als anesthesioloog binnen het Academisch Ziekenhuis Dijkzigt.
Gedurende de opleiding tot anesthesioloog werden er experimenten verricht in het anesthesiologisch laboratorium van de Erasmus Universiteit die tenslotte o.a. tot dit proefschrift hebben geleidt.