Pituitary Adenolysis by Electrocoagulation

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電氣 凝固에 依한 下垂體摘除

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Introduced by Moricca in Rome in 1966, neuroadenolysis of the pituitary gland, commonly referred to as NALP, has been performed with thousands of patients around the world as a non-specific method of relieving cancer pain.

By 1988, this procedure had also been performed in a total of 1,175 cases by 33 hospitals in Japan with good to excellent results in 78%• of the cases.

A similar trend was also confirmed in authors series as presented in the table 1.

In authors series, 125 of 172 procedures or 73 %, resulted in long-lasting pain relief.

Pain free period lasted for six months in average and in several cases, the procedures had repeated up to three times on the recurrence of pain.

Various complications however, were also reported in the world, including those serious complications as total blindness, hypothalamothalamic syndrome, and meningitis. The

Table 1. A Case Review of Chemical Hypophysectomy.(Mar. 1977 to Nov. 1984)

Primary site of cancer	Male	Female	Total	Number of procedures	Complete pain relief	(%)
Breast	1	29	30	41	35	(85)
Prostate	25	–	25	31	26	(84)
Thyroid	0	3	3	3	3	(100)
Sub Total	26	32	58	75	64	(85.3%)
G-I Tract (Oesophag. to Rectum)	31	7	38	49	27	(55)
Uterus	–	4	4	7	4	(57)
Lungs	9	5	14	18	12	(67)
ENT	6	4	10	10	8	(80)
Sarcomas et al	5	3	8	11	9	(82)
Pinealoma	0	1	1	2	1	(50)
Sub Total	51	24	75	97	61	(62.9%)
Grand Total	77	56	133	172	125	(72.7%)

most frequent complications were the transient onset of diabetes insipidus and liquorrhea. Some benign side effects, however, including euphoria and polyphagia, have also been reported.

The incidence of these complications frequently following the procedure became a major detraction to the use of NALP, thus inhibiting the widespread use of the procedure in general clinical applications.

Authors have ever improved the procedure to preclude these complications. The first improvement introduced was to substitute phenol for alcohol as the neurolytic agent. Phenol was selected because it mixes easily with the contrast media. Fluoroscopic guidance might also preclude excessive extravasation of the neurolytics beyond the sella turcica in error.

The neurolytic agent spreads beyond the sella into the third and fourth ventricles of the brain through the cerebral aqueduct.

Lipton[1] has suggested that extravasated neurolytics will stimulate the periaqueductal gray on passing over the aqueduct, resulting in an activation of the descending antinociceptive pathway.

Authors found, however, that there was excellent relief of pain in many cases where the neurolytics were confined inside the sella as shown in the figure 1. As you see in this case there is no extravasation of the neurolytic observed.

Futher, the autopsy revealed that the epithelium and underlying structures of the aqueduct remained intact without any evidence of their participation on them as Lipton suggested.

Meanwhile, in 1984, Yanagida and coworkers[2] reported a transient relief of pain followed by short electrical stimulation of the pituitary gland. According to their hypothesis, electrical stimulation of the pituitary may evoke an activation of the descending antinociceptive pathway via hypothalamothalamic systems. It follows that pain will return shortly after cessation of electrical stimulation.

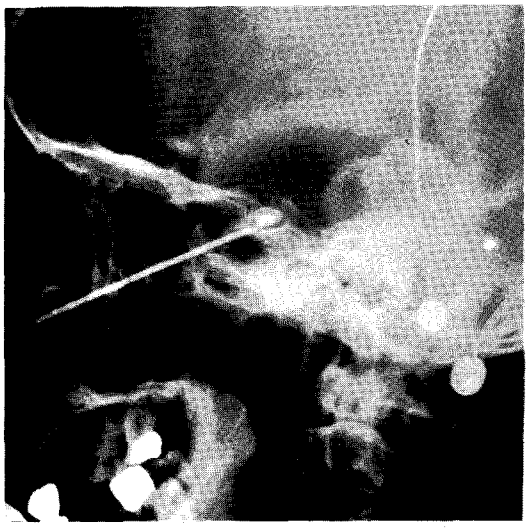

Fig. 1. A case of the X-ray finding shows that the neurolytic agent is confined in the sella without any extravasation.

Authors confirmed their hypothesis in a series of seven cases by electrostimulation using a coaxial bipolar electrode in a needle.

The pituitary was electrically stimulated by a 50Hz square wave pulse, being lasted 0.2 ms and voltage varied from 4 to 9 volts according to individual thresholds. The stimulation was confirmed by the EEG as a series of irregular spikes appeared over regular rhythm. These trains of electrical stimulation produced a transient relief of pain which did not last longer.

After several trials, authors developed a method of inducing electrocoagulation in the pituitary gland using a C-shaped electrode to produce a microthermoinjury of the gland. This injury evoked an injury current lasting a few weeks and stimulating the antinociceptive pathway as if the injury was actually a prolonged electrical stimulation.

Allow us to briefly describe the technique

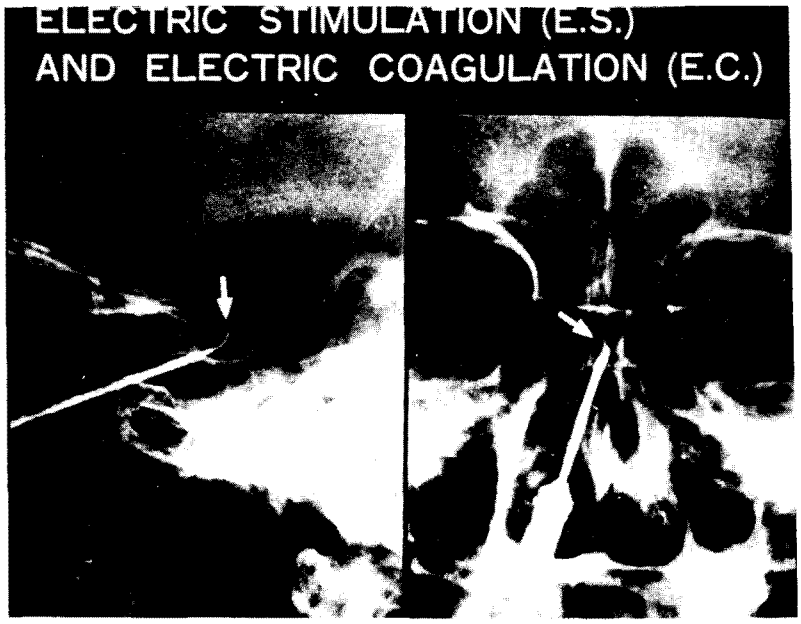

Fig. 2. A case of the X-ray finding shows the location of the electrode in near to the pars intermedia.

used in authors procedure.

In principle, normal patient consciousness was maintained throughout the procedure, giving light sedation with 5 mg Diazepam i.v. as necessary.

Somatosensory evoked potentials(SSEP) were monitored. Following topical analgesia with 4% mepivacaine, the nasal cavity was sterilized by gauze packing soaked with chlorhexidine digluconate in water with epinephrine and antibiotics. The face was then draped after facial sterilization.

Using an X-ray fluoroscope, a 16-gauge electroinsulated needle was inserted through the right nostril into the sphenoidal sinus.

After sterilization of the sinus, the needle was further advanced into the sella. The electrode was guided by the preceding needle.

The electrode tip was placed at the middle of the saggital plane and the center of the pituitary gland near the stereotaxic location of the pars intermedia, as shown in the figure 2.

Electrical stimulation applied through the electrode tip was manipulated to discover that location resulting in alleviation of cancer pain. That site was then coagulated by radio frequency with a tip temperature of 90 degrees centigrade for 60 sec.

The effects of coagulation are confirmed in vitro using an egg white plate and it is comfirmed in vivo as a reduction of tissue impedance.

A review of the outcome of this procedure is presented in the table 2. The electrocoagulation was applied 26 times in 23 cases. In three cases, a second procedure was repeated in a few weeks. Good to excellent results were observed in 78% of all patients.

The lesion was so small that the normal endocrinological functions of the pituitary were maintained completely. Polyuria due to diabetes insipidus was never observed following this pro-

Table 2. A Case Review of the Pituitary Electro-coagulation.(by June 1990)

Primary site of cancer	Male	Female	Total	Total procedure	Result Excellent	good	Poor
Breast		2	2	2	2		
Thyroid		1	1	1		1	
Prostate	1		1	1			1
Sub Total	1	3	4	4	2	1(75%)	1(25%)
Lung	3	1	4	5	1	3	
ENT		2	2	2		2	
G-l Tract	4	6	10	12	4	4	2
Liver & Pancreas	1	1	2	2	1		1
Skin	1		1	1			1
Sub Total	9	10	19	22	6	9(78.9%)	4(21.1%)
Grand Total	10	13	23	26	8	10(78.2%)	5(21.7%)

cedure.

Unfortunately, the duration of the pain-free period was shorter with this coagulative procedure than with NALP, as the injury current may cease within several weeks in some cases due to fibrous healing of the lesion. The longest pain-free period was four months.

Although some degree of pain returned after two weeks in half of the patients, it was possible to reduce the morphine doses to less than half as used before.

Microscopic findings on autopsy of the longest pain free survivor, revealed necrosis primarily in the pars intermedia of the pituitary gland accompanied by necrobiosis in the adjacent anterior lobe. Similar findings were also observed in other cases in which pain was successfully controlled. In order to elucidate its exact mechanism of pain relief, authors investigated changes of the pain threshold induced by this procedure.

Since pain is conveyed by both A-delta and C fibers, authors investigated the change in pain thresholds of the both.

Table 3. The Changes of Pain Thresholds exepressed in Percent as before and after either Successful NALP or Electro-coagulation of the Pituitary Gland.

NALP

Case (n=7)	Radiant heat Min	Radiant heat Max	Tourniquet time
Mean S.E.	128.5% ±5.54*	129.6% ±6.10*	196.5% ±7.56*

COAGULATION

Case (n=7)	Radiant heat Min	Radiant heat Max	Tourniquet time
Mean S.E.	120.5% ±10.4	124.4% ±12.5	226.5% ±21.5**

**P<0.01
*P<0.05

The radiant heat calorimetry was used to evaluated pain threshold via the A-delta with C fibers, and ischemic pain produced by a tourniquet to investigate the pain threshold via C fibers.

In the radiant heat calorimetry test, the caloric value when patient acknowledge a "hot" sensation was designated the minimum threshold, and the value when the arm withdrawn was designated the maximum threshold. The ischemic tolerance time was evaluated by inflating the tourniquet to 300 mmHg on the arm.

Based on pre- and post-NALP and electrocoagulation thresholds, the ischemic tolerance time via C-fibers was significantly prolonged by both procedures as shown in the table 3.

If the cancer pains originated from vascular compression caused by tumor growth, pain relief by both procedures could be explained from the raised pain threshold on ischemia. However, severe pain via the A-delta fibers was not sufficiently suppressed on the findings with the radiant heat method.

In addition, SSEP indicated the subjective changes in the perception and recognition of pain.

In authors study on SSEP, a median nerve was stimulated by suprathreshold potency, and the evoked potentials of the contralateral sensory area on the scalp were summed with the

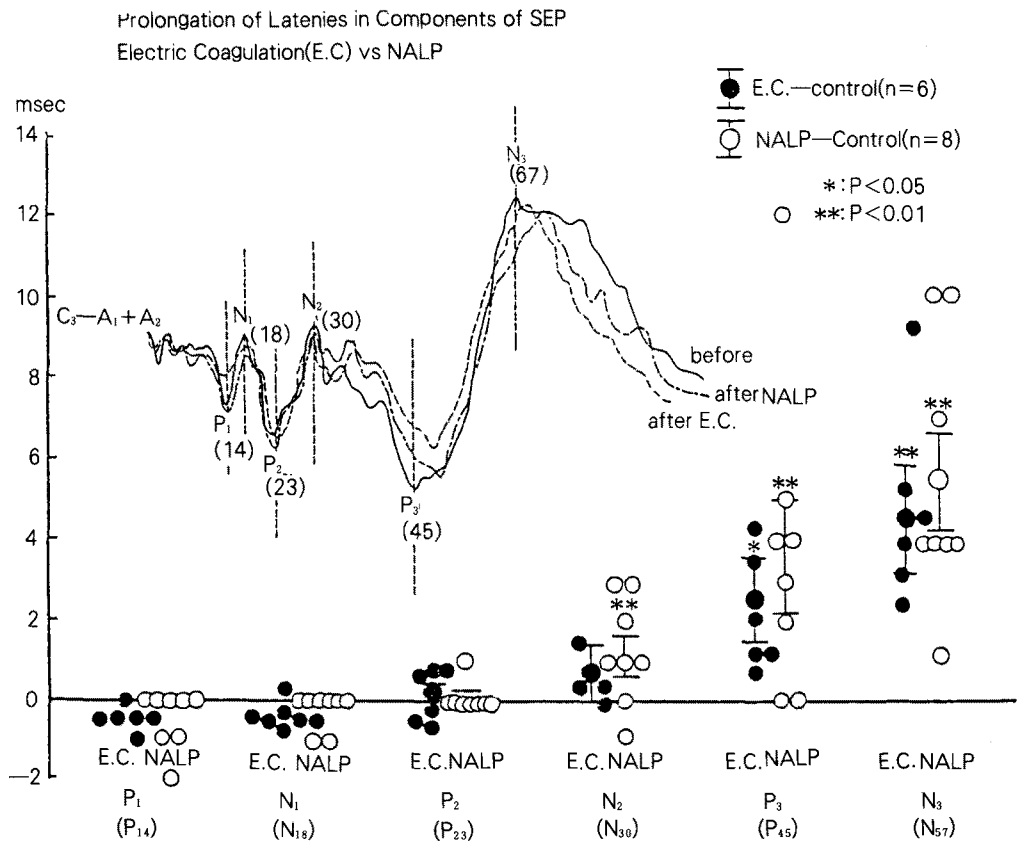

Fig. 3. Changes in components of SSEP before and after either the NALP or the electro-coagulation of the pituitary. The time course upto 100 msec is taken in the abscissa, and the differences in prolongation of latencies is taken as msec in the ordinate.

The filled circle with dotted line denotes electrocoagulation of the pituitary and the open circle with chained line does NALP. The real line means data before the procedure.

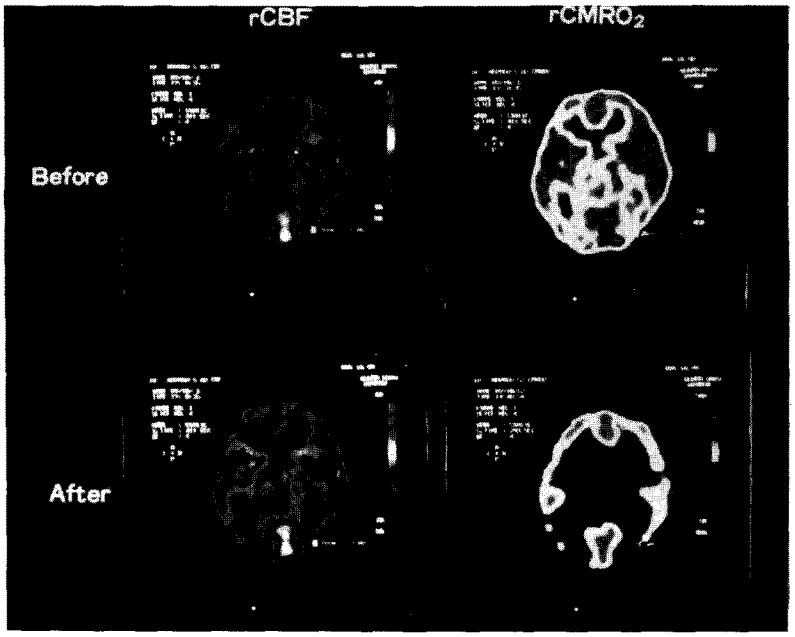

Fig. 4. An image pictures on PET by means of Oxygen-15 to show the regional cerebral blood flow(the left) and the regional cerebral oxygen consumption(the right), before(the upper) and after(the lower) the electrocoagulation of the pituitary.

ipsilateral one serving as its own control.

As shown in the figure 3, when objective pain relief was manifested by the patient, the latencies of long latency components longer than 30 ms on SSEP were prolonged, while the latencies of short components were not affected.

The same thends were observed after NALP. This indicates that both NALP and electrocoagulation would be originated on the same mechanism affecting pain relief, specifically that the perception of pain was not affected, but recognition was disturbed.

To elucidate the mechanism of pain recognition instead of perception in more detail, authors measured regional cerebral blood flow, regional cerebral oxygen consumption, and regional cerebral metabolism.

With the patients' consent and cooperation, these measurements were performed in seven cases under positron emission computerized tomography(PET), before and after the procedure.

As shown in the PET image obtained by Oxygen-15 in the figure 4, there is an overt suppression of diffuse regional cerebral oxygen consumption in the frontoparietotemporal lobes with no consistent change in regional cerebral blood flow before and after NALP.

These findings were confirmed in all cases by the computer analysis.

Regional cerebral metabolism of glucose was also investigated since regional cerebral oxygen consumption is not always reflected by regional cerebral metabolism, because a superior radio active resolution by Fluoride-18 to by Oxygen 15 is able to discriminate it in more accuracy.

A PET image of fluoride-18 dioxyglucose enabled us to analyze the regional cerebral metabolism more precisely before and after the procedure[3].

Table 4. The Changes of the Regional Cerebral Blood Flow and the Regional Cerebral Glucose Metabolism before and after the Successful Electrocoagulation of the Pituitary Gland. (n=7, mena±SE)

Brain structure	rCBF(ml/100 ml/min)			rCMRO$_2$(ml/100 ml/min)		
	Before	After		Before	After	
Frontal cortex	37.0±7.1	33.9±4.1	NS	4.10±0.65	2.47±0.30	P<0.05
Parietal cortex Lt	34.0±5.9	33.6±4.2	NS	4.07±0.63	2.31±0.23	P<0.05
Rt	31.0±4.9	31.3±4.1	NS	4.02±0.68	2.40±0.35	P<0.05
Occipital cortex	34.5±7.5	30.8±3.6	NS	4.08±0.64	2.75±0.50	P<0.05
Basal ganglia Lt	32.8±7.0	29.4±4.1	NS	3.09±0.43	1.81±0.09	P<0.05
Rt	32.9±7.0	28.2±3.5	NS	3.23±0.50	1.75±0.09	P<0.05
While matter	26.4±3.4	26.2±2.8	NS	3.23±0.51	2.08±0.33	P<0.05

N.S.: not significant

The results of quantitative analysis of cerebral glucose metabolism on PET are presented in the table 4. Suppression of cerebral glucose metabolism after the procedure was observed to be 25% in the frontal, parietal, and temporal sections of the cortex.

While no structural suppression has been so far identified, the suppressed metabolism observed in most areas of the brain coincided with that occurring after administration of opioids[4].

If the hypothalamothalamic antinociceptive pathway is activated by stimulation of the pituitary, levels of 8 arginine vasopressin, AVP, should be increased in intracerebral spinal fluid because AVP was a representative hormone released from the hypothalamus.

In authors series, levels of AVP in CSF obtained by spinal tap increased discriminately in cases of relieved pain as presented in the table 5. In unsuccessful cases, whom pain persisted, the elevation of AVP levels was not obvious.

AVP acts as an antidiuretic hormone in blood, but its action in CSF has not been confirmed yet. Bernston and coworkers[5][6] reported an antinociceptive action in rats on instillation of AVP into the cerebral ventricles.

Authors[7] also confirmed the analgesic effect of AVP on monkeys.

Table 5. The Elevated Levels of AVP, Arginine Vasopressin, in CSF after Successful Electrocoagulation of the Pituitary Gland. In Unsuccessful Cases, Levels of AVP in CSF coincided with the Normal Values.

Result	Number of case	Level(pg/ml)
Excellent	7	159.1±52.2(*P<0.05)
Good	5	10. ± 0.4(*P<0.05)
Poor	3	6.1±2.8

*: compared to the pre coagulation levels

Authors evaluated the analgesic effects of AVP in comparison with fentanyl and or kappa agonist after their instillations into the cerebral ventricles of Japanese monkeys in awake. Authors observed the changes of latencies after the instillation on SSEP recorded through electrodes chronically implanted in the epidural spaces.

Arginin-vasopressin as well as fentanyl and kappa-agonist U-50, 488H caused no change in the short-component latencies but prolongation of the late-component latencies was observed 10 min after instillation. An analgesic potency of AVP was evaluated to be the one fourth of

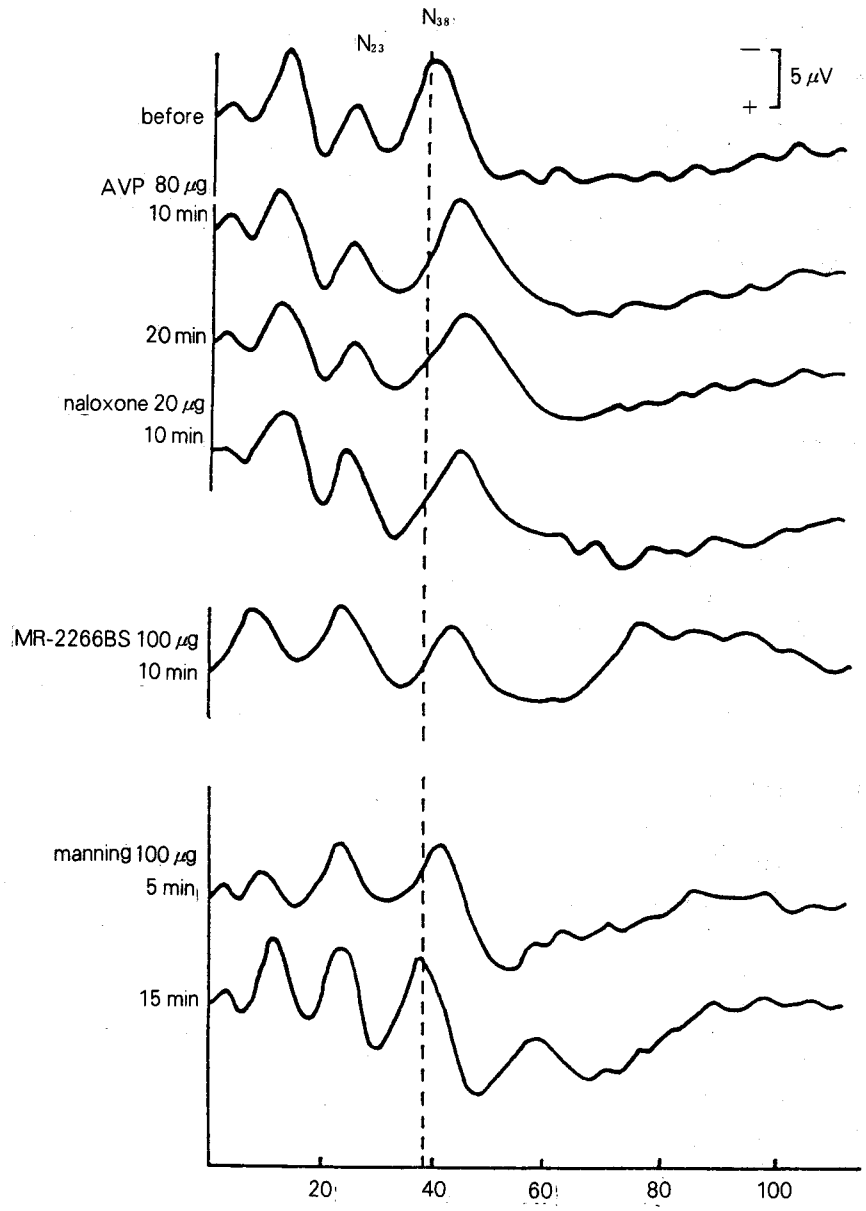

Fig. 5. The changes of latencies in components of SSEP of on a monkey. The time course upto 100 msec is taken in the abscissa.

fentanyl. Changes caused by AVP were neither reversed by a high dose of naloxone nor kappa-antagonist, MR-2266BS. On the other hand by a vasopressin-antagonist 'manning', the changes were completely reversed as shown in the figure 5.

In recent years, it has become clear that vasopressin-containing axons are distributed to a number of sites of those amygdala, lateral septum, mediodorsal thalamus, substantia nigra, and substantia gelatinosa of the spinal cord[8]. They are heavily implicated in pain control,

learning and memory retention. The presence of vasopressin within axon of the central nervous system certainly raises the possibility that vasopressin may act as a neurotransmitter and neuromodulator.

AVP in CSF is secreted from the paraventricule neucleus into the third and lateral ventricles, whereas AVP in plasma is synthe sized in the supraoptic nucleus, transported along the hypothalamus-hypophyseal pathway, stored in the neurohypophysis and released to the blood.

The analgesic mechanism of NALP would be related to a continuous rise in AVP in CSF due to the destruction of the hypothalamus-hypo physeal pathway[9,10].

Based on this study, authors propose that the analgesic effect of AVP is unrelated to the opioid systems, those of mu and kappa, but it may be attributed to the activation of descending antinociceptive pathways.

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