Alterations of Hypothalamopituitary Interaction and Pain Threshold Following Pituitary Neuroadenolysis

—A Clinical Investigation of the Mechanism of Cancer Pain Relief—

Fumikazu TAKEDA, Takashi FUJII, Jiro UKI,
Ryuji TOZAWA*, Yoshiaki FUSE*, Yasuharu KITANI**
and Tatsushi FUJITA**

*Neurosurgery and *Anesthesiology Clinics,
Saitama Cancer Center, Saitama;
**Department of Anesthesiology,
Gunma University, Maebashi*

Abstract

Clinical investigations were carried out to elucidate the mechanism through which pituitary neuroadenolysis (NALP) relieved intractable cancer pain. When investigating hypothalamopituitary interaction, continuous elevation of TRH and arginine vasopressin were observed in the cerebrospinal fluid (CSF) following NALP. ACTH¹⁻³⁹ in the CSF abruptly increased after NALP in cases with complete pain relief, in contrast with the far less elevation in cases without complete relief. There was no significant increase of endorphins in the CSF. The sufficient inactivation of the anterior and posterior pituitary functions indicated the success of the procedure, but had no exact correlation with the obtainability of complete relief of cancer pain, though cancer pain was more frequently alleviated in hormone-dependent carcinomas than in non-dependent.

Valuation of pain responsiveness showed the duration of tourniquet tolerance in cases with complete relief of cancer pain following NALP was twice as long as before NALP, while it was unchanged in cases without complete pain relief. Radiant heat dolorimetry revealed no significant differences between cases with complete pain relief and those without. Sensory decision theory analysis denoted increased pain threshold and improved discriminability in cases with complete relief. Pain threshold determination thus indicated increased C-fiber thresholds, which mainly mediate cancer pain, and excluded the placebo effect of NALP. Observations indicated that the increase of peptides in the CSF, which are mainly synthesized in the hypothalamopituitary axis, would exert a suppressive effect on the mediation and perception of cancer pain through the C-fibers and the central nervous system.

Key words: pituitary neuroadenolysis, cancer pain relief, hypothalamopituitary interaction, cerebrospinal fluid, peptides, pain threshold

Introduction

Instillation of ethanol into the sella turcica, or pituitary neuroadenolysis (NALP), resulted in excellent and long-lasting relief of pain due to disseminated carcinoma metastases from various origins, both hormone-dependent and non-dependent.^{4,12,13,15-19,}

24, 25, 30, 31)

Since 1977, the authors have performed NALP on 102 patients with intractable cancer pain, and obtained satisfactory pain relief in 80% of the cases.^{30, 31)} The procedure has particular advantages in its simplicity and brevity, repeatability in cases of recurrence of pain, excellent rate of acceptance by patients, minimal post-

Received October 6, 1982; Accepted December 6, 1982

Author's present address: T. Fujii, M. D., Department of Neurosurgery, Gunma University School of Medicine, Maebashi, Gunma, Japan.

treatment discomforts, and short hospital stay.^{4,31)} The mechanism by which NALP relieves cancer pain remains to be determined. The authors reported observations on the spread of ethanol instilled into the sella turcica and the resultant morphological changes in the hypothalamopituitary axis.³²⁾ The purpose of this paper is to describe some clues obtained through clinical investigation on the alterations of hypothalamopituitary interaction and of pain threshold following NALP which may elucidate the mechanism of cancer pain relief.

Materials and Methods

NALP was performed 136 times on 102 patients who suffered from intractable pain caused by disseminated metastases of malignant neoplasms. Of these 102 patients, 43 harbored hormone-dependent carcinomas such as carcinomas of the breast, prostate, and thyroid, while the other 59 harbored non-hormone-dependent tumors. NALP was performed twice in 32 cases for recurrent pain and lack of response to the initial NALP, and 3 times in 3 cases for the same reasons. With the aid of televised fluoroscopy, the puncture needle was introduced manually towards the sella turcica through a nostril, and, thus, the pituitary gland was punctured approximately to the midline. Then, 100% ethanol was gently instilled in a total amount of 1.0 to 2.4 ml. The technical aspects and clinical results of cancer pain relief were reported in detail elsewhere.³¹⁾ Complete pain relief, in which no analgesic medication was necessary for over a week, was ultimately achieved in 82 (80%) out of 102 cases: 95% in 43 cases with hormone-dependent carcinomas; and 69% in 59 cases with non-hormone-dependent tumors. Pain relief was immediate in most cases, and continued for a period over 2 years in some cases.

Before and after NALP, the following clinical examinations were carried out to study the alteration in hypothalamopituitary interaction, and the alteration of the pain threshold.

I. Anterior pituitary function

The serum concentration of each anterior pituitary hormone was determined. The resting level of hormone, as well as peak concentration provoked by appropriate stimuli such as insulin, TRH, and LH-RH, were measured by means of radioimmunoassay. The post-NALP determination was commonly carried out 1 to 3 weeks after NALP had been performed.

II. Posterior pituitary function

On urinalysis, the hourly volume, osmotic pressure, and specific gravity were continuously checked in each

case through conscientious management of the water-electrolyte balance to check for polyuria, or diabetes insipidus, which might develop following NALP.

III. Peptides in cerebrospinal fluid (CSF)

CSF was obtained before NALP, 24 hours after, and later on an appropriate day, through a lumbar tap or a ventriculo-peritoneal shunt device, when available. Concentration of ACTH¹⁻³⁹, β -endorphin, TRH, and arginine vasopressin was determined by means of radioimmunoassay. To determine the β -endorphin concentration, CSF was eluted through a sephadex G50 column in 1% formic acid at 4°C to avoid cross reaction of β -LPH (modified Jeffcoate's technique¹⁰⁾).

IV. Pain threshold

Pain threshold was evaluated before and 24 hours after 28 performances of NALP. Evaluation was also made several days after NALP in some of the cases. The methods applied were as follows.

Radiant heat dolorimetry: Wolf-Hardy's dolorimeter, modified by Nakahama, was applied to the patient's forearms, and the maximum radiant heat (435 mcal/cm²/sec) was given in the "timed" threshold method. The patients were requested to inform us when they felt a very faint pain; the time measured up to that point was called the minimum pain threshold (mpt). The time at which they withdrew their arms due to an intolerable sensation of pain was measured and called the maximum pain threshold (MPT). Each post-NALP result was expressed as the percent change of the patient's own control value determined prior to NALP.

Duration of time tolerated under tourniquet: An orthopedic tourniquet was applied to the patient's upper arm and inflated to 500 mmHg. The duration was measured when the ischemic pain became intolerable. The results were also determined by computing the percent of baseline value measured before NALP.

Sensory decision theory (SDT) analysis: Radiant heat stimuli were applied to 12 pre-determined spots on the middle of the volar surface of the patient's forearms. Six intensities of stimuli were used; 0, 120, 240, 305, 370, and 435 mcal/cm²/sec, as described by Clark.³⁾ During each examination, 84 stimuli, 14 at each of the intensities, were applied in a partial random ascending series of intensities with a 3.0 second stimulus duration. Patients categorized each thermal experience according to a 14-response scale³⁶⁾ (Table 5). The non-parametric SDT approach was used to generate measures of discriminability (d') and response bias (B). The d' value was transformed to 2 arcsine square root P (A), [2ARS - P (A)], for statistical analysis. It indexed the patient's ability to distinguish between 2 stimuli of different intensities; the higher the value of d' , the fewer the

errors made by the patients. As stated by Yang *et al.*,³⁶⁾ B located the patient's criterion for reporting pain; a higher value indicated less pain reported.

Results

I. Anterior pituitary function

Measurement before NALP revealed that the secretion of each anterior pituitary hormone was normal in most cases. After NALP, the hormone concentration, both at resting and at peak levels, was commonly decreased to various degree (Fig. 1), except for ACTH¹⁻³⁹, which was significantly elevated at resting and peak levels in half of the cases (Fig. 2). The secretion of TSH, prolactin (PRL), and gonadotropins (LH, FSH) were reliable indicators of pituitary inactivation induced by ethanol instillation, but HGH was less reliable in the post-treatment stage due to the inevitable administration of hydrocortisone. The secretion of prolactin and TSH were fairly suppressed

by the initial NALP, and further inactivated by the second NALP (Fig. 3).

Anterior pituitary function, following 68 initial NALP, was classified into slightly/moderately suppressed and markedly suppressed groups. In the slightly/moderately suppressed group, 85.7% of the cases showed complete pain relief in contrast to 90.9% in the markedly suppressed group (Fig. 4).

II. Posterior pituitary function

Out of 136 NALP performed in 102 cases, 69 induced polyuria, a urinary excretion of more than 3,000 ml/day with lowered urinary osmolarity. The polyuria usually developed within 24 hours after NALP, and abated by the 14th post-treatment day. The observation of hourly urinary volume in the polyuria revealed a rhythmic pattern of urinary excretion, which had been characterized by Fujii *et al.*⁷⁾ in diabetes insipidus following surgical intervention of the pituitary gland. Obtainability of complete pain relief with

Fig. 1 Serum concentration of each anterior pituitary hormone before and after NALP.

Fig. 2 ACTH¹⁻³⁹ concentration in serum before and 1-60 days after NALP.

Fig. 3 Prolactin concentration (resting level) in serum before and after NALP (A 56-year-old female with breast carcinoma).

Fig. 4 Pain relief and anterior pituitary function following NALP.

the 101 initial NALP cases (in 1 case, ethanol instillation was abandoned because of empty sella) was not significantly different in cases with and without polyuria (Fig. 5).

III. Peptides in CSF

ACTH¹⁻³⁹: The curious secretional function of ACTH prompted us to determine the ACTH¹⁻³⁹ concentration in the CSF before and after NALP. Before NALP, the ACTH¹⁻³⁹ concentration in the CSF ranged from 10 to 225 pg/ml. It abruptly elevated to approximately 10,000 pg/ml at 24 hours after in cases with complete relief of cancer pain, while such an

Fig. 5 Pain relief and polyuria after NALP.

Fig. 6 ACTH¹⁻³⁹ concentration in CSF before and 24 hours after NALP.

elevation was not found in cases without complete relief (Fig. 6), but there was an exceptional case. In 2 cases with breast cancer, ACTH¹⁻³⁹ concentrations in the CSF and serum was continuously studied (Fig. 7). CSF was obtained through a ventriculo-peritoneal shunt device, which was placed 2-6 months before NALP for treatment of intracranial cancer metastases. The CSF ACTH¹⁻³⁹ concentration was exceedingly elevated as soon as an hour later, and decreased to almost pre-NALP levels by the second or third post-NALP day, while the ACTH in the serum showed less marked elevation and soon fell to a level below the pre-NALP level. The ACTH concentration stayed at a higher level in the CSF than in the serum, even after 2 months, when the serum concentration was almost undetectable.

β -endorphin: Before NALP, average CSF β -endorphin was 46.87 pg/0.1 ml. In 7 cases measured within 24 hours after NALP, the β -endorphin concentration was higher than pre-NALP levels, but no significant

Fig. 7 Continuous estimation of peptides in CSF after NALP (Case ST). *: not eluted before endorphin assay. **: mcU $\times$ 2.5 $\div$ pg/ml.

Table 1 β -endorphin in CSF before and after NALP (pg/0.1 ml)

Cases	Before NALP	24 hours after NALP	6-50 days after NALP	(days)
MI	UD	115	5	(50)
NS	UD	102	—	
KN	89	109	—	
KT	68	90	—	
EH	74	—	84	(8)
RA	79	—	76	(6)
MF	115	—	94	(6)
ST	UD	53.5	UD	(21)
YI	UD	40	10.5	(13)
KK	55	155	UD	(9)
HS	67	—	98	(24)
Mean $\pm$ SE	46.87 $\pm$ 11.95	94.93 $\pm$ 14.85	45.94 $\pm$ 16.11	

UD: undetectable level (below 5 pg/0.1 ml).

change was apparent 6 to 23 days after NALP (Table 1). The same specimen that was used in continuous determination of ACTH was used to continuously evaluate β -endorphin (Fig. 7). CSF β -endorphin also abruptly rose to an exceedingly high level, almost concomitantly with ACTH. It fell to pre-NALP levels by the third post-treatment day, and decreased to a level lower than that in blood (Fig. 7). The serum concentration of β -endorphin showed less elevation.

TRH: TRH in the CSF, determined before NALP in 12 cases, ranged from 12 to 60 pg/ml, with an average of 29.75 pg/ml. It was almost always elevated 24 hours after NALP and later steadily increased in all of the cases with complete pain relief, as well as in 1 case without complete relief (Table 2). In continuous determination (Fig. 7), TRH abruptly increased in the CSF following NALP, and soon fell to a level above the pre-NALP level. Then, it gradually increased again, demonstrating some rise and fall.

Vasopressin: Arginine vasopressin was determined in the CSF of 12 cases. Before NALP, it was below 3.0 mcU/ml. Following NALP, it was often elevated to a higher level in the first post-treatment day and also 6 to 21 days after NALP in cases with complete pain relief (Table 3), and even in cases showing diabetes insipidus following NALP. Vasopressin was also continuously determined in CSF and serum (Fig. 7). It was abruptly elevated in the CSF immediately after NALP, and then decreased, but remained at a level higher than the pre-NALP level even 3 weeks after NALP. On the other hand, vasopressin in serum did not show any significant elevation and was always lower than in the CSF.

IV. Pain threshold

Radiant heat dolorimetry: In cases with complete pain relief, the mean value of mpt after NALP was 131.0

Table 2 TRH in CSF before and after NALP (pg/ml)

Cases	Before NALP	24 hours after NALP	6-21 days after NALP	(days)
AU	60	—	90	(21)
EH	25	—	35	(8)
FK	30	24	32	(11)
KK	50	40	80	(9)
YI	15	30	80	(13)
SM	40	40	—	
ST	30	80	90	(21)
TT	20	30	—	
CN	12	18	—	
SS	30	40	—	
TR	25	90	—	
MF*	20	30	47	(6)
Mean $\pm$ SE	29.75 $\pm$ 3.99	42.20 $\pm$ 7.39	64.86 $\pm$ 9.77	

*: without complete relief.

$\pm 6.86\%$, and that of MPT was $135.7 \pm 7.26\%$ (Table 4), a percentage taken from the patient's own control. In cases without complete relief, the mean mpt was $122.7 \pm 10.56\%$ and mean MPT was also raised to $115.2 \pm 9.13\%$. These results denote that there were no significant differences between cases with complete relief of cancer pain and those without.

Duration of time tolerated under tourniquet: The mean value of duration under tourniquet following NALP was almost twice as long in cases with complete relief, while it remained unchanged in cases without complete relief (Table 4).

SDT analysis: Mean value of B before NALP was 8.739 ± 0.350 in cases with complete relief,

Table 3 Arginine vasopressin in CSF before and after NALP (mcU/ml**)

Cases	Before NALP	24 hours after NALP	6 days-2 years after NALP	(days)
TR	0.3	43.0	—	
NS	0.3	58.0	—	
KN	0.7	0.8	—	
SM	3.0	2.9	—	
MF	0.9	—	7.3	(6)
HS	0.5	—	5.0	(6)
AU	2.5	—	29.0	(3)
MI	0.9	7.1	0.3	(24)*
YI	1.2	5.8	11.0	(7)
KK	1.7	79.0	24.0	(6)
ST	2.7	54.0	5.7	(21)
KA	—	—	1.2	(2 years)
Mean $\pm$ SE	1.34 $\pm$ 0.29	31.32 $\pm$ 10.87	10.43 $\pm$ 3.72	

*: with recurrent pain at measurement, **: mcU $\times 2.5 \div$ pg/ml.

and rose to a higher threshold after NALP (10.023 ± 0.575). On the other hand, it did not change in most cases without complete relief (Table 6). The discriminability (d') was improved following NALP in most cases with complete relief, and was not improved in cases in which cancer pain was not relieved by NALP (Table 6). These data denote increased pain threshold and improved d' following NALP.

Discussion

The instantaneous relief of cancer pain obtained by NALP would suggest that it was mediated through the central nervous system, rather than through endocrine factors. The sufficient inactivation of the anterior and posterior pituitary functions indicates the success of the procedure, but has no exact correlation with the obtainability of complete pain relief, as has been stated by others.^{15,16} However, endocrinological ablation should be considered to have a possible role as cancer pain was more frequently alleviated in hormone-dependent tumors than in non-dependent.³¹

Most investigators suggest that humoral factors may have a significant role in the achievement of relief from cancer pain. Certain authors^{16,33} suggest the possible role of endorphins, prostaglandin, ADH, and neurophysin. There is much interest in endorphins. Misfeldt *et al.*,²³ Katz and Levin,¹³ and the authors^{30,31} report that administration of naloxone following pituitary ablation is not able to reverse cancer pain. We determined that the increase of endorphins in the CSF after NALP was temporary, and there was no significant change in the CSF concentration of endorphins in the chronic post-treatment stage. Observation indicates that pituitary necrosis induced by ethanol instillation³² cannot result in lasting elevation of CSF endorphins, and also confirms that hypophysectomy fails to depress the concentration of endorphins in the brain.⁶ It seems hardly possible to explain long-lasting pain relief with endorphins, even though they could account for the immediate pain relief. These observations would exclude endorphins from the major mediators in the relief of cancer pain through NALP.

Both endorphins and ACTH have a common precursor,²⁰ and are concomitantly secreted mainly by the pituitary gland.⁹ But, in contrast to endorphins, ACTH¹⁻³⁹ shows not only a marked increase in the early post-NALP stage, but also a higher level in the CSF than in blood, even 2 months later. The patient without immediate increase of ACTH in CSF cannot obtain complete relief of cancer pain. These findings indicate some possible role of ACTH in achieving pain relief through NALP.

Table 4 Percentage change of pain threshold after NALP (pre-NALP value = 100)

Case	Radiant heat dolorimetry		Tourniquet time
	mpt	MPT	
Cases with complete relief			
1	107.7	176.0	137.3
2	169.5	111.1	128.6
3	112.5	139.1	212.5
4	132.8	112.5	122.4
5	115.5	84.3	122.4
6	150.4	153.4	355.5
7	148.5	121.1	166.7
8	152.0	139.1	338.1
9	128.5	133.3	257.1
9*	142.9	181.2	315.8
10	100.0	157.1	127.9
11	102.4	98.1	162.5
12	113.0	122.2	170.6
13	133.3	155.0	250.0
14	104.2	88.8	153.0
15	229.0	212.9	164.2
16	121.4	137.2	104.7
17	112.5	111.5	144.3
18	114.7	135.0	107.3
Mean $\pm$ SE	131.0 $\pm$ 6.86 NS	135.7 $\pm$ 7.26 NS	189.9 $\pm$ 18.31 p > 0.001
Cases without complete relief			
19	111.1	106.3	72.3
20	157.2	142.9	80.7
21	125.0	183.3	112.5
22	107.6	112.0	103.6
23	200.0	101.9	100.0
24	133.3	123.8	107.8
25	122.2	97.2	93.8
26	81.2	70.0	98.4
27	105.3	100.0	113.3
28	84.2	114.5	92.7
Mean $\pm$ SE	122.7 $\pm$ 10.56 NS	115.2 $\pm$ 9.13 NS	97.5 $\pm$ 3.97 NS

mpt: minimum pain threshold, MPT: maximum pain threshold, NS: non-significant, *: after second NALP.

It is reported that ACTH⁴⁻¹⁰ and α -MSH alter behavioral activity and appetitive tasks in experimental animals.^{5, 6, 22, 28)} ACTH and possibly α -MSH may act in some as yet unknown manner in the relief of cancer pain, and it is also suggested that they are possibly derived from a tissue other than the pituitary gland. Tindall *et al.*³³⁾ report that surgical hypophysectomy, removal of the gland which mainly

Table 5 Response scale and its relationship to values of response bias (B)

Value of B	Response scale	Value of B	Response scale
14	nothing	7	faint pain
13	maybe something	6	pain
12	faint warmth	5	very painful
11	warm	4	2.66 – 3.00*
10	hot	3	2.32 – 2.65*
9	very hot	2	2.00 – 2.31*
8	very faint pain	1	= 1.99*

*: withdrawal time (sec.).

secretes the peptides, relieves pain in metastatic cancer other than breast and prostate, and Krieger *et al.*¹⁴⁾ demonstrated high, though dissociated, concentrations of immunoreactive lipotropin and endorphin, as well as ACTH in the bovine hypothalamus, hippocampus, and brain stem. Radioactive α -MSH is also located in various regions of the rat brain.¹¹⁾

The steady increase of TRH in CSF suggests not only feedback from suppressed serum TSH concentration, but also some possible role of the hypothalamic hormone. TRH has some likely effects on the brain other than TSH-releasing activity on the anterior pituitary, and the brain receptors for TRH are considered to differ from those in the pituitary.⁶⁾ Although the concentration is low, calculation leads to the conclusion that only about 20% of the total brain TRH is to be found in the hypothalamus.²⁶⁾ TRH is present in the midbrain, cerebellum, brain stem, and cerebral cortex in rats,³⁵⁾ and extrahypothalamically in the human brain.⁸⁾ The increased CSF concentration of TRH, the hypothalamic peptide, indicates altered function of the hypothalamopituitary axis induced by NALP, and suggests its role in the relief of cancer pain by means of pituitary ablation.

Vasopressin is found to be elevated in the CSF, even in patients showing diabetes insipidus following NALP. There is evidence that relatively few secretory fibers reach the third ventricle, in comparison with those ending on the posterior pituitary lobe.²⁷⁾ Vasopressin has also been reported to occur within neurons terminating in a number of periventricular sites within the limbic forebrain, diencephalon, and mesencephalon.^{2, 29)} The instillation of ethanol into the sella turcica disturbs the transportation of vasopressin toward the posterior pituitary and also its storage, and thus can promote its release into the periventricular area. This might be the reason for the increased concentration of vasopressin in CSF following NALP. Berntson and Berson¹⁾ report that intraventricular

Table 6 Sensory decision theory analysis of pain threshold

Cases		Response bias (B)		Discriminability (d') [2ARS - P (A)]	
		Before NALP	After NALP	Before NALP	After NALP
Cases with complete relief	S-1	10.80	11.30	2.75	2.65
	S-2	9.10	12.50	2.80	2.30
	S-3	8.90	11.50	2.75	2.50
	S-4	8.30	9.30	2.10	2.15
	S-5	8.07	8.43	2.35	2.28
	S-6	7.89	8.83	2.94	2.59
	S-7	8.27	8.80	2.98	2.59
	S-8	8.58	9.52	2.70	2.74
Mean $\pm$ SE		8.739 $\pm$ 0.350 (Difference = 1.28 $\pm$ 0.36, $p < 0.01$)	10.023 $\pm$ 0.575	2.696 $\pm$ 0.119 (Difference = -0.2 $\pm$ 0.09, $p < 0.05$)	2.500 $\pm$ 0.095
Cases without complete relief	S-9	8.80	8.16	3.05	3.10
	S-10	8.50	8.20	2.80	2.70
	S-11	7.80	7.85	2.15	2.25
	S-12	8.65	8.50	2.42	2.45
	S-13	9.50	8.39	2.63	2.27
	S-14	8.58	8.43	2.70	3.01
	S-15	9.52	8.58	2.70	2.94
Mean $\pm$ SE		8.764 $\pm$ 0.245 (Difference = -0.40 $\pm$ 0.18, NS)	8.364 $\pm$ 0.108	2.636 $\pm$ 0.117 (Difference = 0.04 $\pm$ 0.09, NS)	2.674 $\pm$ 0.145

NS: non-significant.

administration of vasopressin is found to induce potent and dose-dependent antinociceptive actions in rats, and analgesia induced by vasopressin is not blocked by naloxone, suggesting that this analgesia is independent of the opiate receptor system. It is also reported that, on a molar basis, vasopressin appears to have approximately one-third the analgesic potency of β -endorphin after intraventricular administration.³⁴⁾ Based on the experimental results with rats, Mens *et al.*²¹⁾ suggest that the mechanisms controlling CSF vasopressin levels is quite different from those affecting the plasma level of this hormone. Lipton¹⁷⁾ states an episode that when diabetes insipidus following NALP was controlled by pitressin, then the pain relief was not as satisfactory, though this observation cannot be confirmed. These reports strongly suggest that the increased CSF vasopressin following NALP may have a role in the relief of cancer pain through NALP. Vasopressin is supposed to exist in a binding form with protein, so that it would not pass the brain-blood barrier.

Pituitary necrosis is a consequence of the ethanol instillation into the sella turcica,³²⁾ and the ethanol

often flows out into the third ventricle.^{17,19,32)} In spite of this finding, morphological alteration of the hypothalamus is not demonstrated except for a localized small necrosis in the infundibulum in 39% of the autopsy cases³²⁾; however, frequent, but temporary, clinical manifestations of euphoria, polyphagia, hyperthermia, and hallucinations indicate hypothalamic involvement with NALP.³¹⁾ It is considered by the authors³²⁾ that the ethanol which flows out into the third ventricle would act as a destructive as well as a stimulative agent on the nervous structures around the ventricle, and that these effects might induce some functional changes.

Radiant heat is supposed to stimulate A δ -fibers and C-fibers, while ischemic pain, induced here with a tourniquet, is considered to mediate *via* C-fibers. The pain threshold determination revealed an increased threshold of pain sensation *via* C-fibers following NALP, which mainly mediate cancer pain. It may be possible to explain cancer pain relief through the prolonged tourniquet tolerance time. The SDT analysis also showed an increased pain threshold, and, moreover, improved discriminability. These findings in pain

threshold determination also indicate that the patients were psychologically unaffected, excluding a possible placebo effect of NALP.

The clinical investigations presented in this paper, still in progress, indicate that significant increases of ACTH, TRH, and vasopressin are induced by NALP. These peptides are mainly synthesized in the hypothalamopituitary axis and their changes represent the NALP-induced alteration of the hypothalamopituitary interaction. Though the exact physiological activity of peptides in pain sensation still remains obscure, their increase in the CSF, along with suppressed pituitary functions, is considered to exert a suppressive effect on the mediation and perception of cancer pain through the C-fibers and the central nervous system.

Acknowledgment

The authors sincerely express their appreciation to Prof. T. Mitsuma, the Department of Internal Medicine, Aichi Medical University, for TRH determination. Part of this work was presented at the Annual Meeting of Japan Neurosurgical Society, 1981, Kyoto; at the 3rd World Congress of Pain, 1981, Edinburgh; at the 1st International Symposium on Pain, 1981, Verona; at the 6th Asian-Australasian Congress of Anesthesiology, 1982, Auckland, New Zealand; and at the 13th International Cancer Congress (UICC), 1982, Seattle.

References

- Berntson GG, Berson BS: Antinociceptive effects of intraventricular or systemic administration of vasopressin in the rat. *Life Sci* 26: 455-459, 1980
- Buijs RM, Swaab DF, Dogterom J, van Leeuwen FW: Intra- and extrahypothalamic vasopressin and oxytocin pathways in the rat. *Cell Tissue Res* 186: 423-433, 1978
- Clark WC: Pain sensitivity and the report of pain: An introduction to sensory decision theory. *Anesthesiology* 40: 272-287, 1974
- Corssen G, Holcomb MC, Moussetapha I, Langford K, Vitek JJ, Ceballos R: Alcohol-induced adenolysis of the pituitary gland: A new approach to control of intractable cancer pain. *Anesth Analg (Cleve)* 56: 414-421, 1977
- de Wied D, Bohus B, van Ree JM, Urban I: Behavioral and electrophysiological aspects of peptides related to lipotropin (β -LPH). *J Pharmacol Exp Ther* 204: 570-580, 1978
- Donovan BT: The behavioral actions of the hypothalamic peptides: A review. *Psychol Med* 8: 305-316, 1978
- Fujii T, Misumi S, Takeda F: Diurnal patterns of urinary excretion during polyuria after the pituitary surgery and its management. *Neurol Med Chir (Tokyo)* 21: 1105-1112, 1981 (in Japanese)
- Guansing AR, Murk LM: Distribution of thyrotropin-releasing hormone in human brain. *Horm Metab Res* 8: 493-494, 1976
- Guillemin R, Vargo T, Rossier J, Minick S, Ling N, Rivier C, Vale W, Bloom F: β -endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. *Science* 197: 1367-1369, 1977
- Jeffcoate WJ, Rees LH, McLoughlin L, Ratter SJ, Hope J, Lowry PJ, Besser GM: β -endorphin in human cerebrospinal fluid. *Lancet* II: 119-121, 1978
- Kastin AJ, Nissen C, Nikolics K, Medzihradsky K, Coy DH, Teplan I, Schalley AV: Distribution of ^3H - α -MSH in rat brain. *Brain Res Bull* 1: 1-21, 1976
- Katz J, Levin AB: Treatment of diffuse metastatic cancer pain by instillation of alcohol into the sella turcica. *Anesthesiology* 46: 115-121, 1977
- Katz J, Levin AB: Long-term follow-up study of chemical hypophysectomy and additional cases. *Anesthesiology* 51: 167-169, 1979
- Krieger DT, Liotta A, Suda T, Palkovits M, Brownstein MJ: Presence of immunoassayable β -lipotropin in bovine brain and spinal cord: Lack of concordance with ACTH concentrations. *Biochem Biophys Res Commun* 76: 930-936, 1977
- Levin AB, Benson Jr RC, Katz J, Nilsson T: Chemical hypophysectomy for bone pain in carcinoma of the prostate. *J Urol* 119: 517-521, 1978
- Levin AB, Benson RC, Katz J: Treatment of diffuse metastatic cancer pain by stereotaxic chemical hypophysectomy: Long-term results and observations of mechanism of actions. *Pain Abstract* 1(Second World Congress on Pain): 293, 1978
- Lipton S: *Relief of Pain in Clinical Practice*. Oxford, Blackwell Scientific, 1979, pp 178-220
- Lipton S: *The Control of Chronic Pain, Current Topics in Anaesthesia Series 2*. London, Edward Arnold, 1979, pp 104-107
- Lipton S, Miles J, Williams N, Bark-Jones N: Pituitary injection of alcohol for widespread cancer pain. *Pain* 5: 73-82, 1978
- Mains R, Eipper BA, Ling N: Common precursor to corticotropin and endorphins. *Proc Natl Acad Sci USA* 74: 3014-3018, 1977
- Mens WBJ, Bouman HJ, Bakker EAD, van Wimersma Greidanus TB: Differential effects of various stimuli on AVP levels in blood and cerebrospinal fluid. *Eur J Pharmacol* 68: 89-92, 1980
- Miller LH, Kastin AJ, Sandman CA: Psychobiological actions of MSH in man. *Front Horm Res* 4: 153-161, 1977
- Misfeldt DS, Goldstein A: Hypophysectomy relieves pain not via endorphins. *N Engl J Med* 297: 1236-1237, 1977
- Moricca G: Neuroadenolysis for the antalgic treatment of advanced cancer patients, in Bonica JJ, Procacci P, Pagni CA (eds): *Recent Advances on Pain*. Springfield, CC Thomas, 1974, pp 313-328

- 25) Moricca G: Chemical hypophysectomy for cancer pain, in Bonica JJ (ed): *Advances in Neurology*, vol 4, *International Symposium on Pain*. New York, Raven, 1974, pp 707-714
- 26) Reichlin S, Saperstein R, Jackson IMD, Boyd AE, Patel Y: Hypothalamic hormones. *Ann Rev Physiol* 38: 389-424, 1976
- 27) Rodriguez EM: Morphological and functional relationships between the hypothalamo-neurohypophyseal system and cerebrospinal fluid, in Bargmann W, Scharrer B (eds): *Aspects of Neuroendocrinology, V International Symposium on Neurosecretion*. Berlin, Springer, 1970, pp 352-365
- 28) Sandman CA, George J, McCanne TR, Nolan JD, Kaswan JK, Kastin AJ: MSH/ACTH4-10 influences behavioral and physiological measures of attention. *J Clin Endocrinol Metab* 44: 884-891, 1977
- 29) Swanson LW: Immunohistochemical evidence for a neurophysin-containing autonomic pathway arising in the paraventricular nucleus of the hypothalamus. *Brain Res* 128: 346-353, 1977
- 30) Takeda F: Results of pain relief and tumor regression by pituitary neuroadenolysis and surgical hypophysectomy, in Ischia S, Lipton S, Maffezzoli GF (eds): *Pituitary Neuroadenolysis in Cancer Pain and Hormone-Dependent Tumors*. Verona, Edizioni Libreria Cortina Verona (in press)
- 31) Takeda F, Fujii T, Uki J, Fuse Y, Tozawa R, Kitani Y, Fujita T: Cancer pain relief and tumor regression by means of pituitary neuroadenolysis and surgical hypophysectomy. *Neurol Med Chir (Tokyo)* 23: 41-49, 1983
- 32) Takeda F, Uki J, Fujii T, Kitani Y, Fujita T: Pituitary neuroadenolysis to relieve cancer pain: Observation of spread of ethanol instilled into the sella turcica and subsequent changes of the hypothalamopituitary axis at autopsy. *Neurol Med Chir (Tokyo)* 23: 50-54, 1983
- 33) Tindall GT, Nixon DW, Christy JH, Neill J: Pain relief in metastatic cancer other than breast and prostate gland following transsphenoidal hypophysectomy. A preliminary report. *J Neurosurg* 47: 659-662, 1977
- 34) Walker JM, Sandman CA, Berntson GG, McGivern RF, Coy DH, Kastin AJ: *Pharmacol Biochem Behav* 1: 543-548, 1977, cited from 1)
- 35) Wilber JF, Montoya E, Plotnikoff NP, White WF, Gendrich R, Renaud L, Martin JB: Gonadotropin-releasing hormone and thyrotropin-releasing hormone: Distribution and effects in the central nervous systems. *Recent Prog Horm Res* 32: 117-159, 1976
- 36) Yang JC, Clark WC, Ngai SH, Berkowitz BA, Spector S: Analgesic action and pharmacokinetics of morphine and diazepam in man: An evaluation by sensory decision theory. *Anesthesiology* 51: 495-502, 1979

Address reprint requests to: F. Takeda, M. D., Neurosurgery Clinic, Saitama Cancer Center, 818 Komuro, Ina-machi, Kitaadachi-gun, Saitama 362, Japan.