[Workshop]

**Third International Workshop of
UOEH on
Emotion and Higher Nervous Function**

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at

Ramazzini Hall

University of Occupational and Environmental Health, Japan

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University of Occupational and Environmental Health, Japan

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Preface

Ladies and gentlemen,

On behalf of the members of the University of Occupational and Environmental Health, Japan, I am very happy to welcome you to this workshop. Before you begin your activities, I would like to tell you some special characteristics of our university.

The extremely rapid achievement of modern industry has actuated a development based on the materialistic element in our society. This is also true in the area of medicine in Japan and it is widely accepted that Japanese medicine has attained the topmost level in the world.

However, beneath the surface of this industrialized world, the nations as well as their citizens are threatened by an increase of undesirable health inhibitors produced by the complexities of our highly industrialized life. Particularly in Japan, partly because of our too rapid industrial expansion, we have lagged behind a few countries in providing the working people with a higher quality of life. This has incited the Ministry of Labor to establish a university for the purpose of promoting occupational health and educating physicians and other occupational health personnel as well as researchers who are to work in the area of occupational health.

Thus, it was decided to establish the University of Occupational and Environmental Health, Japan (UOEH), including both undergraduate and postgraduate schools.

The university was established in 1978. This university includes five schools (School of Medicine, Graduate School of Medical Science, School of Nursing, School of Medical Technology and School of Occupational and Community Health Nursing), and one University Hospital as well as one institute. The institute was established in April 1986, and was named the "Institute of Industrial Ecological Sciences." The aims of the University of Occupational and Environmental Health, Japan are as follows:

1. The University will educate medical and health professionals to educate themselves and to have as their lifelong philosophy a devotion to serving the health needs of humanity.
2. By focusing attention on the occupational and general environment of man, the university will endeavor to develop and integrate the field of environmental science with life science.
3. The university will strive to develop a new discipline of ecology which will incorporate economic considerations.
4. The university will not only firmly establish occupational and environmental health in an industrialized and post-industrial society, but will also integrate it into comprehensive community health services.

The university, as a pioneer in the field of the medical and health sciences in the 21st

century, will strive to accomplish these goals for the purpose of establishing a new society and a better life for all.

Lastly, I am sure that you will have a successful workshop and I hope that you will enjoy your stay in Kitakyushu.

Thank you.

Osamu KOIDE, M. D.

Vice President of the University of Occupational
and Environmental Health, Japan

Introduction

On October 16, 1989 the Third International Workshop was held at the Ramazzini Hall of UOEH. This series of workshops were found to be quite successful in contributing to an international exchange of ideas and quick dissemination of recent developments in various fields. The first workshop was held in 1984, the second in 1988. The third conference was aimed at exploring difficult but very significant areas of research, namely, emotion and higher nervous function, and was characterized by participants who are interested in many aspects of physiological science.

In two morning sessions studies on emotions from the behavioral and psychosocial standpoint (Drs. Corson and Majkowski), and on changes in EEG and the intriguing hemispheric dominance relating to the subject (Drs. Matsuoka and Yamadori) were presented. At the cellular level, papers reporting work on hippocampal neurons in various behaviors (Dr. Ono) and on brainstem neurons during sexual behavior (Dr. Shimokochi) were of great interest. Metabolic changes related to stress (Dr. Nicolov) were also reported.

After enjoying a lunch in the garden behind the auditorium, two more sessions followed. The new aspect of brain mechanisms of our age-old problems, such as oxytocin secretion (Dr. G. Leng) and thirst and drinking (Drs. Ramsay and Koizumi), were discussed. Topics on the most recently developed fields were also covered; the papers included the physiological significances of fibroblast growth factor (Dr. Oomura), the central actions of immune-cytokines (Dr. Hori) and the action of various peptides on hypothalamic neurons (Dr. Yamashita).

Closing remarks were made by Dr. Shigeaki Matsuoka, Professor of Neurosurgery of UOEH and a member of the organizing committee, who contributed greatly to the success of this symposium. Since he will retire from UOEH in the spring, this may be the last opportunity for me to work together with him in meetings like this. I wish to express my gratitude for his help during the past number of years.

This workshop provided a small international group of scientists an occasion to exchange our recent results, help each other to solve our problems and plan our future directions. The atmosphere was friendly and intimate, allowing critical comments to be easily exchanged. Scientific discussion as well as pleasant conversation continued till late in the evening at Amagase spa.

All participants in the workshop express deep gratitude to President Kenzaburo Tsuchiya who has supported the meeting generously. We also wish to express our appreciation to members of the Department of Physiology.

Hiroshi Yamashita
Organizer and Editor

1. Dr. S. Matsuoka	10. Dr. G. Leng	19. Dr. D. A. Ramsay
2. Dr. J. Majkowski	11. Dr. N. A. Nicolov	20. Dr. T. Hori
3. Dr. K. Koizumi	12. Dr. Y. Oomura	21. Dr. N. Akamatsu
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Topographic EEG Study of Visual Display Terminal (VDT) Performance with Special Reference to Frontal Midline Theta Waves

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Operators of visual display terminals (VDT) often complain of physical, as well as psychological stress. Under certain circumstances, an increased psychological stress among VDT operators is seen to create serious problems in their occupations, yet few studies have dealt directly with this problem. It is not clear how such it should be measured and evaluated. We report the results of experiments where psychological stress was induced during VDT tasks such as visual search and computer mouse operation tasks. The relationship between spatio-temporal analysis of EEG activity and productivity of VDT work was investigated.

The subjects were divided into three age groups: young adults (18–22 years old), middle aged (38–42 years old) and the elderly (58 years and over). Characteristic EEG changes occurred during VDT tasks. These consisted of frontal midline theta waves with maximum amplitude at Fz. Statistically significant relationships were found between duration of working, EEG electrode location on the head, as well as correlations between work speed and variation of theta waves.

It is concluded that some factors relating to the severity of a mental task and the distribution of cortical EEG potentials are closely related. When long lasting theta waves appear in the EEG, a rest period should be considered, before the subjects complain of fatigue. An effective method to determine the duration of work and rest periods can be designed using the EEG.

Emotion and the Right Hemisphere

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Until recently functions of the right hemisphere have been considered to be very difficult to define. However the recent development in the field of neuropsychology drastically

changed this situation. One of the many functions recently attributed to the right hemisphere is emotion. For instance patients with right hemisphere damage tend to be indifferent to their surroundings (Gainotti, 1969), or become aprosodic in their speech (Ross, 1981). We present three kinds of neuropsychological observations which further support the contention that the right hemisphere is involved in emotional functions.

The first observation is a frequent occurrence of "agitated delirium" during the acute stroke with a lesion limited to the right hemisphere. The acute agitated delirium is characterized by confusion and emotional changes with vivid hallucination, delusion, affective excitement and autonomic hyperactivity. We were able to diagnose six cases of acute agitated delirium out of 41 consecutive cases with the acute infarctions of the right middle cerebral artery territory. Damage of the right middle temporal gyrus seemed to be responsible for the syndrome (Mori & Yamadori, 1987).

The second observation concerns with the well-known syndrome of anosognosia of the Babinski type. This classical syndrome is characterized by a patient's peculiar unconcern or even denial of the the existence of paralysis in the left side of his body. Six typical cases of anosognosia that we collected showed common behavioral features besides anosognosia, i. e., loss of facial expression, monotonous speech, inattention towards the surroundings and indifference to one's own physical status. In short, they became flat in their emotional life. All six patients had lesions in the right perisylvian area (Yamadori, 1989).

The third observation is a single case. A 55-year-old right handed female suddenly developed confusion and left hemiplegia. An immediate CT scan of the brain demonstrated a hemorrhage in the putamen of the right hemisphere. A peculiar point worth reporting in this patient is that she became very euphoric. She would sing in bed without any embarrassment. She would even sing ad libitum in front of an examining physician. This euphoria with singing subsided in about 2 weeks. We have had no such cases with the left hemisphere stroke.

It is clear from these observations that the damage to the right hemisphere does produce emotional change. It could be agitation, flattening or euphoria. From the abundant animal and clinical data, there seems to be a remote possibility that the right hemisphere is directly responsible for emotional life. The limbic system is far more important in this respect. Rather, the right hemisphere may have a function as a kind of modulator in expressing and receiving emotional signal.

References

- Gainotti, G. (1969): Reactions "catastrophiques" et manifestation d'indifference au cours des atteintes cerebrales. *Neuropsychologia*, 7 : 195-204.
- Mori, E. & Yamadori, A. (1987): Acute confusional state and acute agitated delirium. Occurrence after infarction in the right middle cerebral artery territory. *Arch. Neurol.*, 44 : 1139-1143.
- Ross, E. D. (1981): The aprosodias; functional-anatomic organization of the affective components of language in the right hemisphere. *Arch. Neurol.*, 38 : 561-569.
- Yamadori, A. (1989): Anosognosia. *Neurol. Med. (Tokyo)*, 30 : 364-369.

A Systems Approach to the Study of Visceral Orienting Reflexes as Indices of Homeokinetic Stability

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On the basis of a prospective systems-designed study of psychophysiologic reactions of 70 dogs (of different breeds) to a psychologically aversive environment, we discovered two major types of dogs: 1) Low Adaptation dogs (LA) which exhibited a complex pattern of psychophysiologic and neuroendocrine distress reactions which persisted for years even in extinction sessions. 2) High Adaptation dogs (HA) which exhibited only temporary mild psychophysiologic and neuroendocrine reactions. Retrospective analysis of cardiac and respiratory orienting reaction (OR) revealed that the dynamics of the development and extinction of OR could serve as indices of homeokinetic stability and as predictors of the LA and HA classification. The LA dogs exhibited more intense, persistent, and highly fluctuating (poorly modulated) cardiac and respiratory OR than the HA dogs which showed less intense OR responses, good modulation, and rapid OR habituation. It is suggested that 1) the LA dogs may represent a psychophysiologic substrate of type A behavior in humans and 2) the dynamics of the development and extinction of OR in humans may facilitate early detection of individuals at risk for homeokinetic instability and susceptibility to psychovisceral disorders. This may make it possible to initiate early preventive psychotherapeutic measures and to offer early vocational guidance. Supported in part by NIH grant HL 20861, the Ohio State University Graduate School Biomedical Research Support Grant, and the Psychiatric Research Foundation of Columbus.

Aggressive Behavior Related to Epileptic EEG Activity

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Epileptic mechanisms have frequently been proposed as a cause of anger, outbursts, rage, violence, or aggressive behavior in the episodic dyscontrol syndrome or in the temporal lobe behavior syndrome, in persons with or without other symptoms of epilepsy or other neurological problems. Epileptic psychoses with violent, aggressive behavior associated most frequently with epileptiform paroxysmal discharges, or with increased synchronized

theta activity while awake or during natural sleep or narcoleptic attacks have been reported by many authors. Emotional stress is the most frequent triggering factor in partial complex seizures, and the most frequent emotion associated with epileptic discharge in the temporal lobe is fear.

Episodic aggressive behavior related to epilepsy and to specific temporal lobe dysfunction can be divided into the following three groups.

1. Those related directly to the seizures or to epilepsy, namely, the epileptic clouded states in (A) absence status epilepticus or (B) psychomotor status epilepticus and (C) non-ictal states due to direct and widespread interference of cortical function by the ictal discharge.

2. Inter-ictal psychoses not directly related to seizures: (A) with primary mood disorders or (B) schizophrenia-like psychoses.

3. Low threshold for aggression.

Group 1A. In this group of psychoses, aggressive acts are very rare. EEG shows continuous generalized spike and slow wave complexes.

Group 1B. In this group aggression as an ictal form rarely occurs, but it is more frequent than in the previous group. The EEG shows mixed continuous sharp waves, spikes and slow wave activity, predominantly in temporal regions on one or both sides.

Group 1C. States of postseizure confusion. Aggressive behavior which occurs post-ictally is an acute organic psychosis. It results from the patient's misinterpretation of usually well meaning attempts to protect him from the consequences of his confused behavior.

Clouded status often follows a series of seizures and is especially common after an episode of generalized tonic-clonic status epilepticus; it is more common in males (2/3), and in patients whose seizure frequency is more than one major attack a week. The clouding is a direct result of diffuse inhibition of neuronal function which invariably follows seizure discharges. It is manifested in the EEG by diffuse slowing, but is more prolonged than after a single grand mal seizure.

Group 2. Inter-ictal psychoses. In contrast to the psychoses directly related to ictal events, the inter-ictal psychoses result from a more complex interaction of causative factors: biological, psychological and social.

Group 2A. Psychoses with primary mood disorders have a longer duration (week-months) than the clouded states. The onset is not significantly related to seizure, unlike clouded states, but frequently is ended by seizure. Usually, prior to occurrence of these (depressive) psychoses, seizure frequency decreases by 50%.

Group 2B. Schizophrenia-like psychoses. In 2/3 of the schizophrenia-like psychoses, there is clinical and EEG evidence for temporal lobe epileptic activity. The mean age of onset of epilepsy is at puberty and the mean age of psychoses is about 30 years. Psychoses are developed on an average of about 15 years after the seizure. They occur in 2% of epilepticus.

Schizophrenia-like psychosis is an epileptic psychosis directly due to the temporal lobe epilepsy. The etiological relationship results from limbic system dysfunction caused by the temporal lobe epileptogenic activity. Years of subclinical disruption of function by continuous inter-ictal, irregular and excessive neuronal firing forms the physiological basis of the psychological disorders which may lead to the appearance of psychoses. The kindling mechanism is proposed in these psychoses. The condition sine qua non of their occurrence is primary or secondary temporalization.

Group 3. Aggressive episodic behavior in temporal lobe epilepsy characterized by a low rage threshold. These patients, in response to the most trifling provocation, may go into a violent rage which is totally out of proportion to the triviality of the triggering event.

α ANP, Immunoreactive Insulin, Blood Glucose and Cyclic AMP in Normotensive and Spontaneously Hypertensive Rats Subjected to Restraint Stress

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Hypertension is more frequently found in patients with diabetes mellitus than in subjects with normal glucose tolerance. On the other hand plasma glucose levels were found to be significantly higher in hypertensives in normotensives. Data concerning blood glucose level in SHR are controversial. Some investigators point to elevated blood glucose in SHR strain while others find no difference from normal rats.

Plasma levels of ANP are found to be abnormal in hypertensives and in some patients with diabetes mellitus. ANP is significantly higher in the hypertensives than in normal subjects, and in diabetic patients higher BP is found more frequently when ANP is higher. In SHR the level of circulating ANP is found to increase and the atrial content to decrease in the course of the developing of hypertension.

In this study we evaluated in both normotensive Wister rats and in SHR the influence of restraint stress on plasma α -ANP, immunoreactive insulin (IRI), blood glucose and cAMP.

Results

α -ANP. The mean plasma ANP concentrations in non-stressed SHR were higher (913.2 ± 111 pg/ml) than in normal WR (493.2 ± 157.2 pg/ml). In SHRSP it was 392.4 ± 93.6 pg/ml. In WR subjected to a 24h restraint plasma ANP levels tended to elevate to

605.7 ± 133 pg/ml ($P > 0.05$) while in SHR subjected to stress plasma ANP markedly decreased to 33.9 ± 13.7 pg/ml ($P < 0.001$), and in SHRSP it tended to decrease to 198.0 ± 67.9 pg/ml.

IRI. Basal serum IRI (in non-stressed groups) of normal WR was 48.58 ± 7.58 pmol/l. In SHR IRI was significantly higher 103.64 ± 8.25 pmol/l ($P < 0.01$) and in SHRSP it was 101.01 ± 4.85 pmol/l ($P < 0.01$) respectively. Restraint stress increased significantly IRI in WR to 86.42 ± 8.81 pmol/l ($P < 0.001$) while in SHR under stress IRI tended to decrease to 75.36 pmol/l and in SHRSP to 95.36 ± 8.48 pmol/l respectively.

Blood glucose level. Blood glucose level in the control Wister group was 4.83 ± 0.33 mmol/l. In non-stressed SHR it was 5.07 ± 0.24 mmol/l. In SHRSP it was 5.6 ± 0.14 mmol/l and was significantly higher than in WR ($P < 0.05$). Restraint stress resulted in a significant elevation of blood glucose in the following three groups: in WR to 7.32 ± 0.68 mmol/l; in SHR to 7.16 ± 0.48 mmol/l and in SHRSP to 11.38 ± 0.53 mmol/l.

Cyclic AMP. Under basal conditions (non-stressed) cAMP in plasma of normal WR was 43.6 ± 8.2 nmol/l. In SHR and SHRSP, basal levels of plasma cAMP were significantly higher: 126.3 ± 24.2 nmol/l and 193.8 ± 28.0 nmol/l respectively. After a 24h restraint stress cAMP in WR showed a tendency to decrease to 38.0 ± 2.9 nmol/l, while in SHR and SHRSP stress resulted in a significant decrease in cAMP plasma level: to 39.6 ± 7.4 nmol/l and to 8.7 ± 2.7 nmol/l respectively.

Conclusions

1. The results of this study point to significant differences in the tested parameters between rats with spontaneous hypertension and normal WR in basal conditions (non-stressed) as well as in their response to restraint stress.
2. The levels of α -ANP, insulin, blood glucose and cAMP are higher in hypertensive rats compared with WR in the control groups.
3. Restraint stress in SHR resulted in a decrease in α -ANP, insulin and cAMP, while in WR these parameters either increased (insulin), or a tendency toward elevation was observed (α -ANP).
4. The higher insulin level and elevated blood glucose point to a disturbance in the glucose metabolism in SHR and SHRSP. Under stress conditions however the elevation of blood glucose accompanied with a tendency of serum insulin to decrease does not give an evidence for a peripheral insulin resistance in these strains.

Responses of Single Neurons in the Monkey Hippocampus during Space Recognition

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Hippocampal involvement in the processing of mammalian's spatial information is now widely accepted. However, there have been no reports of neurons (place cells) that differentiate the location of a primate in space. In the present study, single neuron activity in the monkey hippocampus was recorded during bar press to manipulate a mobile device. A monkey sat in a halfmirrored cabin that could move linearly and rotate. The monkey could control light, sound and temperature in the cabin by change of position (internal environment). The laboratory light was switched on or off (external environment). One of five cue tones predicted a trial. After a short delay food or an object was placed where the monkey could see it. By pressing the appropriate levers, it could move some distance to get the food or a drop of juice.

Of 104 neurons analyzed, 72 responded to some tasks. Of these, 24 were place recognition related (place cells). Place cells fired in response to selective form and spatially directed vision only in a restricted part of the place field. In about 50% of the place cells, these responses were dependent on a synergistical combination of both external or internal environmental cues, and allocentric or egocentric cues. Twenty-one direction selective neurons responded maximally when either the experimenter or the monkey moved to a specific position. Responses to cabin rotation were allocentric, egocentric or reduced. The results suggest that hippocampal involvement in spatial memory is defined by each coordinate of self location, and also by external and internal environment.

A Difference in Firing Pattern between the Medial Preoptic Area and Midbrain Tegmentum during Copulatory Behavior in Rats.

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From lesion and electrical stimulation studies it is suggested that the medial preoptic area (MPO) as well as the lateral mesencephalic tegmentum (LTM) is essential for the initiation of male copulatory behavior of the rat. However, the difference between the two

in the control manner of the male copulatory behavior has not yet been fully understood. In a series of experiments, we recorded single neuron activities from these two regions during free copulatory behavior of male rats.

Two different kinds of neurons were found to be involved in the pursuit-mounting behavior in the MPO; one increased in firing rate continuously during pursuit of a female (pursuit neuron) and the other increased only during pelvic thrusting (thrust neuron). These findings support the notion that the MPO is involved in both sexual motivation and consummatory elements of the sexual response repertoire of the male rat.

In the LTM, on the other hand, four types of firing patterns were observed around pursuit-mounting behavior: 1) The firing ratio increased concurrently with pursuit of a female but decreased just before intromission down to the baseline level. 2) It increased only during pelvic thrusting accompanying intromission. 3) It decreased only during pelvic thrusting. 4) It increased during genital grooming. Thus each LMT neuron may relate to the execution of each repertoire of various copulatory movements.

Although prior experience may play an important role for later copulation in rodents, relatively little is known of the neural mechanisms underlying such behavioral alterations attributed to experience. In a separate experiment, we examined whether the conditioned change in neuronal pattern of the MPO was observed or not by female-rewarded operant learning. For conditioning, we used a cage which was divided into two compartments by a shutter. In the first place, an experimental male and an estrous female were separated in the compartments. Then, the male was trained to approach the shutter in response to a cue tone to trap the female. After about three training sessions, the male began to approach the shutter immediately on the cue tone. By further reinforcement the conditional change was established in a firing of a 'pursuit neuron': when the overt approach behavior was fully conditioned, only that neuron fired about three times more than the pre-tone baseline level in response to the cue tone. Since this increased firing was not associated with any overt movements, it might reflect conditioned sexual arousal produced by the male. This finding further supports the hypothesis that the MPO is involved in sexual motivation.

Pathways in the Control of Oxytocin Secretion

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Oxytocin and vasopressin are secreted into the systemic circulation from neurosecretory terminals in the posterior pituitary. The cell bodies of origin of these terminals are the

magnocellular neurones of the supraoptic and paraventricular nuclei. These neurones are innervated by afferent pathways deriving from circumventricular structures, believed to be involved in monitoring blood-borne signals, and by pathways carrying information derived from vagal and spinal afferent pathways. Oxytocin in the rat is released in response to suckling and during parturition, and in response to changes in plasma osmotic pressure, gastric distension, and a variety of satiety- or nausea-inducing agents such as cholecystokinin (CCK). Much of the input deriving from circumventricular brain regions is channelled through the so-called 'AV3V region'-the region adjacent to the antero-ventral extent of the third ventricle. Lesion of this area impairs the capacity of the oxytocin system to respond to changes in plasma osmotic pressure (Leng *et al.*, 1989) but do not prevent the release of oxytocin in response to suckling (Blackburn *et al.*, 1987), during parturition (Russell *et al.*, 1989) or in response to peripheral injection of CCK (Blackburn & Leng, 1990). Peripheral injection of CCK results in increased noradrenaline release in the supraoptic and paraventricular nuclei (G. Leng, K. Kendrick & T. Higuchi, unpublished results). This result is surprising since CCK injection is a selective stimulus for the release of oxytocin, while noradrenaline release in the supraoptic nucleus is also elevated during haemorrhage (Kendrick & Leng, 1988) which is a relatively more powerful stimulus for vasopressin release. Furthermore, the majority of the noradrenergic inputs seem to innervate the vasopressin-rich areas of the magnocellular nuclei more densely than oxytocin-rich areas. One possible interpretation is that CCK and haemorrhage activate two different noradrenergic systems-haemorrhage acting through the dense A1 projection upon vasopressin cells, while CCK acts through a separate projection possibly from the A2 cell group.

References

- Blackburn, R. E. & Leng, G. (1990): Ablation of the region anterior and ventral to the third ventricle (AV3V region) in the rat does not abolish the release of oxytocin in response to systemic cholecystokinin. *Brain Research* (in press).
- Blackburn, R. E., Leng, G. & Russell, J. A. (1987): Control of magnocellular oxytocin neurones by the region anterior and ventral to the third ventricle (AV3V region) in rats. *J. Endocrinol.*, 144 : 253-261.
- Kendrick, K. M. & Leng, G. (1988): Haemorrhage induced release of noradrenaline, 5-hydroxytryptamine and uric acid in the supraoptic nucleus of the rat, measured by dialysis. *Brain Res.*, 440 : 402-406.
- Leng, G., Blackburn, R. E., Dyball, R. E. J. *et al.* (1989): Role of anterior peri-third ventricular structures in the regulation of supraoptic neuronal activity and neurohypophyseal hormone secretion in the rat. *J. Neuroendocrinology*, 1 : 35-46.
- Russell, J. A., Blackburn, R. E. & Leng, G. (1989): Ablation of the region anterior and ventral to the third ventricle (AV3V region) does not impede parturition in rats. *J. Endocrinol.*, 121 : 109-115.

Fibroblast Growth Factor: its Physiological Action

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We discovered the feeding control substances from the blood. The concentrations of certain sugar acids in blood fluctuate around the μM level as the state of the organism varies between hunger and satiation. Three of these substances are:

(S)-3,4-Dihydroxybutanoic acid γ -lactone(3,4-DB), 2-Buten-4-olide(2-B-4-0), and (2S,4S)-2,4,5-Trihydroxypentanoic acid γ lactone.

The first two induce satiety and the third induces eating behavior. This third substance dose-responsively increases the amount of food eaten whether administered centrally or peripherally in physiological concentration. The satiety substance, 3,4-DB is effective when administered centrally but not when applied by a peripheral route. However, 2-B-4-0, in which a hydroxyl group is absent at the third carbon of 3,4-DB, effectively suppresses food intake by intraperitoneal, intragastric, or by central application. The origin of satiety inducing substances is glutamic acid and that of the hunger inducing substance is glucose. All three produce their effects through the glucose responsive neurons in the lateral and ventromedial regions of the hypothalamus.

Next we found satiety inducing substance, acidic fibroblast growth factor (aFGF), in cerebrospinal fluid. Its concentration increases more than 10 times during the first 2 hours after the start of eating, and it does not again return to the baseline level until about 5 hours after a full meal. The concentration of aFGF also increases after the injection of glucose into the third cerebroventricle. *In situ* hybridization using cDNA to determine mRNA for aFGF showed that aFGF is produced in ependymal cells of the cerebroventricle wall. Staining with polyclonal antibodies showed that during feeding it is released into the parenchyma from whence it diffuses to hypothalamic cells that are related to the feeding process, and to hippocampal and amygdalar cells. Acidic FGF was found to suppress food intake dose-dependently by depressing the activity of glucose-sensitive neurons in the lateral hypothalamus through the activation of protein kinase C.

Acidic FGF is known as a potent mitogen for smooth muscle cells in blood vessels and endothelial cells in capillaries, and as an inducing agent of atherosclerosis. However, damage to hippocampal CA1 cells was prevented by aFGF when ischemia caused damage to them in the absence of aFGF. Passive avoidance (latency to enter a dark region, a preferred location except for the presence of electric shock) was significantly increased by glucose application into the third cerebroventricle. This presumably, was due to memory enhancement or recall induced by the glucose production of aFGF. Avoidance (latency) was lower (Shorter) at times other than two hours after the glucose application, and at any time

after saline control application.

The effective intracerebroventricular dose of aFGF, 80 fmol to 8 pmol per rat, is believed to make it, by far, the most potent, non-toxic suppressor of feeding yet found in the normal mammalian body.

Actions of Immune Cytokines on the Glucose-responsive Neurons in the Rat Ventromedial Hypothalamus

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Immunological cells-derived cytokines such as interleukin-1 (IL-1), interferon α (IFN α) and tumor necrosis factor (TNF) are now known to be synthesized in the brain from glial cells and probably from neurons. Besides the activation of immune functions, these cytokines produce a wide variety of non-immunological host defence responses of central and peripheral origins. Among these responses, fever, anorexia, induction of slow wave sleep and analgesia are taken as CNS-mediated responses. We have previously shown that IL-1 and IFN α produce fever, at least partly, by their actions on the thermosensitive neurons of preoptic and anterior hypothalamus (PO/AH) (Hori, *et al.*, 1988; Nakashima *et al.*, 1988; Nakashima *et al.*, 1989). Anorexia is also one of the commonly observed symptoms during various infections and clinical therapy with interferon. In this study we investigated single activity of glucose-responsive neurons of ventromedial hypothalamus (VMH) in the rat's tissue slices during perfusion of recombinant human IL-1 β (rhIL-1 β) and recombinant human IFN α (rhIFN α).

While the majority of VMH neurons which increased the activity to a rise in glucose concentration were excited by perfusion of rhIL-1 β (40–160 ng/ml) and rhIFN α (100–5000 U/ml), the neurons which increased the activity to a fall in glucose concentration were inhibited by rhIL-1 β and rhIFN α . The majority of glucose-unresponsive neurons were not affected by the cytokines. These neuronal responses are appropriate in explaining the anorexia induced by IL-1 and IFN α . Concurrent application of sodium salicylate, an inhibitor of cyclooxygenase, blocked the rhIL-1 β induced activity of VMH neurons, but not the rhIFN α -induced neuronal activity. This indicates that the actions of IL-1 on VMH neurons requires the local synthesis of eicosanoids.

Alpha melanocyte stimulating hormone (α MSH) (8×10^{-9} – 6.4×10^{-7} M) which is presumed to be an endogenous antipyretic in the brain and a possible antagonist of IL-1 at lymphocytes (Lipton & Clark, 1986; Cannon *et al.*, 1986) specifically depressed the responses to rhIL-1 β of VMH neurons, but not those to rhIFN α . The influence of α

MSH on the IL-1 induced alteration of activities of both neurons and immunological cells suggests that α MSH is an endogenous antagonist of IL-1 at both neurons and immunological cells, and probably works to limit the IL-1 mediated host defence responses such as inflammation, immunological activation and changes in homeostatic functions like anorexia and fever.

As had been shown in the PO/AH thermosensitive neurons (Nakashima *et al.*, 1988), naloxone could block the responses of VMH neurons to rhIFN α , suggesting the opiate receptor mediation of IFN α 's actions on the hypothalamic neurons. The opiate receptor mediation of IFN α 's actions has also been demonstrated in the splenic natural killer cells (Kay *et al.*, 1984). These findings add further evidence showing that some neurons and some immunological cells share the common ligands and common receptor mechanisms, and provide one of the basis of mutual "communication" between the brain and the immune system.

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References

- Cannon, J. G., Tatro, J. B., Reichlin, S. *et al.* (1986): α melanocyte stimulating hormone inhibits immunostimulatory and inflammatory actions of interleukin 1. *J. Immunol.*, 137 : 2232–2236.
- Hori, T., Shibata, M., Nakashima, T. *et al.* (1988): Effects of interleukin-1 and arachidonate on the preoptic and anterior hypothalamic neurons. *Brain Res. Bull.*, 20 : 75–82.
- Kay, N. E., Allen, J. & Morley, J. E. (1984): Endorphins stimulate normal human peripheral blood lymphocyte natural killer activity. *Life Sci.*, 35 : 53–59.
- Lipton, J. M. & Clark, W. G. (1986): Neurotransmitters in temperature control. *Ann. Rev. Physiol.*, 48 : 613–623.
- Nakashima, T., Hori, T., Kuriyama, K. *et al.* (1988): Effects of interferon- α on the activity of preoptic thermosensitive neurons in tissue slices. *Brain Res.*, 454 : 361–367.
- Nakashima, T., Hori, T., Mori, T. *et al.* (1989): Recombinant human interleukin-1 β alters the activity of preoptic thermosensitive neurons in vitro. *Brain Res. Bull.*, 23 : 209–213.

Does Thirst Matter ?

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Water is lost on a continuous basis at variable rates by a number of routes, principally the lungs, skin and urine. Fluid intake is dependent on thirst mechanisms, skin and urine. Fluid intake is dependent on thirst mechanisms, and experimentally can be shown to be proportional to the fluid deficit. Although drinking behavior depends on a number of other factors, such as food intake, hedonistic qualities of fluid additives and learning, basic physiological mechanisms form the template which controls water intake. The normal animal elaborates a concentrated urine, a sign that water conservation mechanisms are active, drinks intermittently and maintains a plasma osmolality which rarely varies by more than 1–2%.

There is good evidence that plasma osmolality is dependent on the integrity of osmoreceptors in forebrain circumventricular organs. In dogs, the organum vasculosum laminae terminalis (OVLT) is important, and discrete lesions of this region cause loss of drinking and vasopressin secretion to raised plasma osmolality, but not other stimuli. Reduced extracellular fluid (or plasma) volume stimulate thirst via cardiopulmonary and arterial baroreceptors and the renin/angiotensin system, but this stimulus is less potent than raised plasma osmolality. For example, following water deprivation in dogs, 70% of the thirst which develops can be attributed to raised plasma osmolality. When access to water is allowed, the animals rapidly consume an amount appropriate to repair the deficit. During drinking, oropharyngeal inputs are important in metering the volume drunk and is suppressing vasopressin secretion prior to absorption of ingested fluid from the gastrointestinal tract.

If inadequate quantities of water are injected, this has profound effects on sodium balance. Thus during water deprivation there is a marked natriuresis which helps to minimize increases in plasma osmolality. In dogs and sheep with OVLT lesions, the dehydration natriuresis is blocked and plasma osmolality may rise 2–3 times that in normal animals during water deprivation, emphasizing the homeostatic importance of the increased sodium excretion. Again, in dogs with chronic thoracic caval constriction, partial restriction of water intake causes natriuresis and amelioration of the raised extracellular fluid volume and peritoneal ascites. The mechanism of the natriuresis awaits clarification, but depends in part on inhibition of angiotensin II stimulated aldosterone secretion by raised plasma sodium.

Thus thirst is accurately controlled and develops in proportion to fluid deficits. Inadequate fluid intake is linked to the regulation of sodium balance in an integrated man-

ner to prevent large changes in plasma osmolality.

Search for Mechanisms of the Primary Polydipsia in the Inbred Mice

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The extremely polydipsic inbred strain of mice, STR/N, having no abnormality in vasopressin secretion and functions of the kidney and other glands show a normal diurnal pattern of ingestive behavior, but their daily water intake reaches as much as 30 to 50 ml, compared to 3 to 7 ml in their controls, STR/1N and Swiss/Webster strains. Our previous studies indicated that the central angiotenin II and the brain opioid system are involved in the primary polydipsia (Koizumi, 1989). In continuing this work we found evidence that the kappa-opioid receptors in the brain play an important role in causing the polydipsia.

Intracerebroventricular (i. c. v.) injection of the specific kappa-opioid antagonist, nor-binaltorphimine (nor-BNI), at less than 1 μ g strongly attenuated drinking nearly to the "normal" level only in the polydipsic strain of mice. Moreover, unlike the action of naltrexone administered i. c. v., nor-BNI did not affect food intake of any strain of mice at the dosage which was effective for reducing the polydipsia (Katafuchi, *et al.*, 1990).

Local injections of naltrexone as well as nor-BNI into the paraventricular nucleus of the hypothalamus (PVN) also attenuated the polydipsia at a much lower dosage than that used for i. c. v. administration. Studies using brain slice preparations showed that the PVN neurons of the polydipsic as well as control strains of mice were inhibited by morphine added to the perfusate, but the threshold for this action was higher (10^{-8} to 10^{-7} M) in the polydipsic than that in the control mice (10^{-9} to 10^{-8} M). A number of PVN neurons inhibited by morphine (10^{-6} M) was slightly less in the polydipsic mice (44%), compared to that in controls (62%). On the other hand, dynorphin similarly applied inhibited a much less number of PVN neurons in the polydipsic strain (25%), while in control mice a larger number of neurons (70%) were inhibited at the same concentration (10^{-6} M). This suggests a different action of the kappa agonist from that of the mu type opiate on these hypothalamic neurons (Nagatomo, *et al.*, 1989).

In conclusion, we wish to propose the hypothesis that in the inbred strain, some type of change occurred in the kappa opiate receptors in the brain which may contribute to the polydipsia, and that the site of its action may be near or in the surrounding areas of the PVN.

References

- Katafuchi, T., Hattori, Y., Nagatomo, I. *et al.* (1990): Kappa opioid antagonist strongly attenuated drinking genetically polydipsic mice. Submitted for publication.
- Koizumi, K. (1989): The primary polydipsia of inbred mice and the opiate system. *J. UOEH*, 11: 109–110.
- Nagatomo, I., Katafuchi, T. & Koizumi, K. (1989): Role of paraventricular nucleus mediating opiates' action on polydipsia. *Soc. Neurosci. Abstr.* 15: 897.

Endothelin Excites Neurons in the Anteroventral Third Ventricle (AV3V) Region of Rat Hypothalamic Slice Preparations

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The region of the anteroventral third ventricle (AV3V) in the hypothalamus may be tightly related to regulation of the autonomic nervous system. Endothelin (ET) is a novel and potent vasoconstrictor peptide isolated from vascular endothelial cells. High affinity binding sites of ET were observed in the central nervous system (CNS). Intracerebroventricular injection of ET increased blood pressure suggesting that ET may be involved in central cardiovascular regulation. To clarify actions of ET on the CNS, extracellular recordings were made from neurons in the region of the AV3V in rat hypothalamic slice preparations. ET-3, which is rat type of ET, was applied to the AV3V neurons by adding the drug to the perfusing medium. Of 80 AV3V neurons tested, 14 (18%) were excited, 4 (5%) slightly inhibited and 62 (77%) were unaffected by ET at 10^{-7} M. The threshold concentration for evoking the excitatory response in the AV3V neurons was approximately 10^{-8} M. Most neurons which were excited by ET were found in the rostral part of the AV3V region and near the region of the organum vasculosum of the lamina terminalis (OVLT). Excitatory responses to ET were also observed in Ca^{2+} free medium. These results suggest that ET excites directly AV3V neurons and acts as a neurotransmitter or a neuromodulator in the CNS and that a part of the ET responses in the CNS is not related with a calcium-related mechanism.