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US-Japan Joint Seminar on Central Control of Eating and Obesity

MEETING REPORT

Obesity refers to excessive body weight due to an accumulation of fat which is usually attributed to overeating and rarely to other factors. Because some individuals can apparently eat much more than others without any resultant increase in fat, other regulating functions involving the endocrine glands, gastrointestinal tract, and hereditary factors must be implicated in food metabolism. The abnormal increase in body weight of at least 15 to 20 percent, characteristic of obesity represents fat, increases in lipocyte proliferation or mass or both. Although gluttony cannot be the only cause of obesity, decreased food consumption seems to be the only certain method for the reduction of body weight.

An attractive and commonly held belief is that some cells of the brain respond to the same signals which govern the accumulation of fat in the lipocyte and control appetite. The signals are complex and seem to indicate changes in the lipid to protein ratio which reflect both body composition in addition to mass. The neurons of the alleged lipid/protein sensing device within the brain regulate motor excitability and thereby determine the organism's responsiveness to external stimulation.

The most common cause of obesity might be conceived as a behavior disorder where environmental stimuli augment the internal conditions which precede eating and result in excessive consumption of food and caloric fluids. Actually relatively little scientific progress has been made in the understanding and control of eating in man and the management of body weight and composition. The use of anorexogenic agents and stimulants must be carefully controlled and even their indiscriminant use could hardly compensate for the effectiveness of a multitude of environmental stimuli continuously present which tend to elicit ingestive behavior particularly in the absence of other competing activities characteristic of modern industrialized societies. Obesity is an important problem and the hypothalamus is definitely involved in the control of ingestion, temperature regulation, lactation, body metabolism and the storage of fat, and the control of motor activity – many of the relevant factors in the determination of body composition and mass.

The hypothalamus and its relations to other parts of the brain appears to be the most logical system to examine for normal mechanisms which underlie excessive intakes under so-called normal conditions which must result from a neural interaction between the internal signals related to metabolism, storage of fat, changes in blood composition, taste and other receptors of the gastrointestinal tract, proprioceptors and potent external cues such as olfactory stimulation and associated visual and auditory stimuli. An examination of the relevant neural pathways and chemical transmitters involved and the modulation of activity within these systems by orogastrointestinal and other peripheral hormonal and humoral factors associated with deposits of adipose tissue and metabolic activity was the subject of a United States and Japan Cooperative Science Program Seminar held at the East West Center at the University of Hawaii in Honolulu on January 6 through 10, 1975, which was entitled *Central Neural Control of Eating and Obesity* and was supported through the National Science Foundation and the Japanese Society for the Promotion of Science.

Professor T. Ban, Osaka University Medical School, in the opening lecture presented a summary of the autonomic functions of the septo-preoptico-hypothalamic system and the major fiber connections of the hypothalamus. Anatomical connections were visualized by means of Marchi and Nauta methods. Physiological functions elicited by brain electrical stimulation included blood pressure, blood sugar, ovulation, gastric motility, respiratory movement, milk ejection, urinary bladder response, and morphological changes in the pituitary. The organization and functional properties of pontine and limbic afferent paths to the hypothalamus were discussed by Professor J. Sutin of Emory University. The ventromedial hypothalamic nucleus seems to be the major source of modulatory input to the lateral hypothalamus. Afferent activation is usually simple with a high degree of convergence of afferent paths. Descending hypothalamic output activates with strong synaptic drive midbrain neurons which are not spontaneously active and do not respond to arousing stimuli and with weak synaptic drive midbrain neurons that are spontaneously active and are excited by peripheral arousing stimuli. Three effects of basolateral amygdaloid stimulation on ventromedial hypothalamic neurons were described; i.e. excitation, inhibition, and disinhibition and discussed in terms of a tentative neuronal network by Professor T. Ono of Kanazawa University. An electrophysiological study of the functional relations between the frontal cortex and the hypothalamus which revealed a definite columnar arrangement of cell groups within the lateral hypothalamus was presented by Professor Y. Oomura of Kyushu University. An electron microscope study of the fiber connections between the frontal cortex and ventromedial and lateral hypothalamus by Professor T. Yamamoto also of Kyushu University revealed: (1) typical degeneration of axons and axon terminals in the neuropils of the ipsilateral frontal cortex from ventromedial and lateral hypothalamic lesions and (2) no obvious degeneration in the ventromedial and lateral hypothalamus following le-

sions in the frontal cortex. These results suggest that neurons of the ventromedial and lateral hypothalamus send axons to the ipsilateral frontal cortex and make direct synaptic contacts with the dendritic spine and shaft of the frontal cortical neurons.

A quantitative analysis of hypothalamic innervation by cholinergic, gabaergic, and catecholaminergic nerve fibers by Professor K. Kataoka of Ehime University demonstrated not only marked regional differences in neural transmitters but also convincing evidence that the marker synthesizing enzymes are localized in the nerve terminals. A comparison of the effects of intracranial administration of 6-hydroxydopamine and guanethidine sulphate on catecholamine depletion, utilizing both light and electron microscopy, and consummatory behavior was presented by Professor G. Singer of LaTrobe University in Australia. Results indicated considerable general tissue damage and serious questions were raised during the discussion concerning the specificity of 6-hydroxydopamine and its use in the future. A film on push-pull chronic perfusion and transfusion techniques in the monkey was shown by Professor R. Myers of Purdue University. Thin layer chromatographic and GC-mass spectrograph analyses of perfusate during eating indicate complex biochemical changes involving many unknown factors such as several amino acids, sugars, and possibly polypeptides in addition to the well known amines. An attempt to explain long term regulation of feeding and energy balance in terms of intracellular utilization of glucose in the ventromedial hypothalamus was made by Professor J. Panksepp of Bowling Green State University. The ventromedial hypothalamus apparently retains nutrients more than the rest of the brain and feeding seems to be correlated with the gradual metabolism of these stores. Professor Y. Oomura of Kyushu University demonstrated that the lateral hypothalamic chemosensitive neuron is usually inhibited by glucose which activates the electrogenic sodium pump and produces a hyperpolarization and is facilitated by free fatty acid which probably inhibits the uptake of glucose and results in a depolarization of the membrane. These cells also display some specific receptor properties for insulin which enhances their discharge rate. Glucoreceptor neurons of the ventromedial hypothalamus which increase in discharge frequency during the application of glucose are inhibited by free fatty acid. The effects of dietary essential amino acids, which produce a centrally mediated anorexia when fed in disproportionate amounts, on single brain cell electrical activity in the lateral hypothalamus and several other parts of the brain were reported by Professor M. Wayner of Syracuse University. Results indicate regional differences and greater sensitivity in cells of the lateral hypothalamus and zona incerta as compared to the thalamus and cerebral cortex.

Effects of changes in blood sugar and intravenous administration of 2-deoxy-D-glucose on electrical activity of efferent nerve fibers innervating the adrenal gland and pancreas were described by Professor A. Niijima of Niigata University. Results were explained in terms of a servo-control loop regulation of blood sugar levels. Unequivocal evidence was presented by Professor G. Smith that cholecystokinin is one factor in the mediation of intestinal satiety. Gastrin has a slight effect but secretin and pancreatic glucagon appear to have no satiety effects under present experimental conditions. Professor D. Porte of the University of Washington and the VA Hospital in Seattle summarized available evidence concerning the neural control of the endocrine pancreas and the secretion of insulin and glucagon. Triglyceride metabolism in epididymal adipose tissue of obese animals was discussed by Professor Okuda of Ehime University. In addition the mechanisms of action of adrenaline and ACTH, with specific emphasis on the role of calcium, were described. Lipid mobilizing substances of the hypothalamus and pituitary were discussed by Professor A. Kastin of Tulane University and the New Orleans VA Hospital. The fact that hypothalamic factors have effects on non-pituitary tissue was emphasized. Dr. D. Nance of UCLA discussed neurohormonal determinants of sex differences in hypothalamic regulation of feeding and body weight. The possibility that the ventromedial hypothalamic nucelus might be the primary neural site for the organizational effects of androgens on the brain was also discussed. The role of sensory factors in chewing and eating was described by Professor Y. Kawamura of Osaka University. An analysis in terms of taste and other oral afferents, cerebral cortex, and hypothalamic mechanisms was presented. Specific sequential changes in the activity patterns of lateral hypothalamic neurons related to lever pressing for food and eating were described by Professor T. Ono of Kanazawa University.

Because the meetings were arranged as an informal seminar, considerable discussion accompanied each presentation. Several topics such as problems in choice and use of terminology, set point theory, the relevance of current neuroanatomy, electrophysiology, and neurochemistry to eating and relations to obesity received special attention. The proceedings will appear as a monograph supplement to *Pharmacology, Biochemistry and Behavior,* published by Ankho International Inc., P. O. Box 65, Phoenix, NY 13135, U. S. A.

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