International Behavioral Neuroscience Society – Ninth Meeting

Neurochemistry of feeding

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The neurochemistry of feeding was a highlight of this meeting. A number of peptides are now known to participate in the control of nutrient balance, and many of them featured in the meeting, including the feeding suppressors α-melanocyte-stimulating hormone, leptin and corticotrophin releasing hormone, and the orexigenic agents, melanin-concentrating hormone, Agouti-related peptide, orexin A and neuropeptide Y. Other substances that play a role in feeding are amylin and its antagonist, AC-187, histamine, dopamine, serotonin, opiates, galanin and CART peptides. The hypothalamic and extrahypothalamic localization of these feeding-related substances and their interactions with one another, and other brain regions, are beginning to be understood. Another symposium focused on σ receptor ligands, such as (+)-pentazocine, PRE-084, the neurosteroid pregnanolone sulfate, NE-100, igmesine (JO-1784) and BD-1008 and related compounds. Results showed that σ ligands may affect Ca^{2+} signaling via two modes of action, one being at the endoplasmic reticulum and the other at the plasma membrane. σ Receptors have been implicated in learning and memory, and may play a role in anxiety and depression.

Introduction

The International Behavioral Neuroscience Society (IBNS) was founded in 1992 to encourage research and education in the field of behavioral neuroscience, and has approximately 575 members from 33 countries, consisting of scientists, clinicians, teachers and others with a background and interest in the relationship between brain and behavior. Attendees numbered about 130 and came mostly from university departments of various disciplines including neuroscientists, with some delegates from industry or government laboratories.

The meeting included a number of symposia, oral sessions, poster sessions and keynote addresses. Presentations covered a range of topics including feeding, neuro-development and plasticity, therapeutic opportunities for σ receptor ligands, stress, anxiety, autism, learning and memory. In a number of cases, new information about drugs or potential drug targets was presented.

Neurochemical control of feeding

Leptin

Leptin decreases food intake, probably by stimulating production of the hypothalamic peptide, α-melanocyte stimulating hormone (α-MSH). Dr Shiraishi reported that glucose-sensitive lateral hypothalamic neurons are inhibited by leptin applied microiontophoretically. Dr Y Oomura (Toyama University, Fukuoka, Japan) studied the response of paraventricular and ventromedial hypothalamic glucosensitive neurons to leptin and found them to be stimulated. Leptin also facilitated learning and long-term potentiation of the hippocampus, suggesting a role for this peptide beyond the control of feeding. Corticotrophin releasing hormone (CRH) decreases feeding in the same manner as α-MSH and leptin, and inhibits lateral hypothalamic glucosensitive neurons while melanin-concentrating hormone (MCH) is synthesized in lateral hypothalamic neurons stimulates feeding in rats. Dr Shiraishi reported that lateral hypothalamic neurons are activated by microiontophoretic application of MCH.

Agrp

Agouti-related peptide (Agrp) was named after a mutant mouse strain that produces high levels of this protein and is obese. It is produced in cells of the arcuate nucleus and opposes the action of α-MSH. Agrp activates lateral hypothalamic glucosensitive neurons and stimulates feeding. Dr MM Hagan (University of Cincinnati Medical Center, OH, USA) reported that the melanocortin receptor (MC-R) agonist, MTII (Merck & Co Inc) decreased feeding when injected into the third ventricle. Co-injection of Agrp blocked this effect. Furthermore, co-injection of the opioid antagonist, naloxone, with Agrp blocked its orexigenic effect, meaning that the appetite enhancing effects of Agrp are mediated by MC-R antagonism and interaction with μ/κ opioid receptors.

NPY

Neuropeptide Y (NPY) neurons can be found in the arcuate nucleus of the hypothalamus. Dr K Sasaki (Toyama University, Toyama, Japan) recorded from arcuate neurons and found that their firing rate was increased by orexin and decreased by leptin or NPY. The action of NPY was attributed to auto-inhibition of the NPY-ergic neurons by their own collaterals.

Dr SF Liebowitz (Rockefeller University, New York NY, USA) reported that, under some circumstances, consumption of a carbohydrate diet stimulates NPY in the arcuate and paraventricular nuclei. Results suggest a feed-forward mechanism that may lead to over consumption. Dr A Levine (Minnesota Obesity Center, VA Medical Center, Minneapolis, MN, USA) added that NPY levels in the arcuate and paraventricular nuclei increase with food deprivation.

Histamine

Histaminergic neurons are found in the brain in the mammillary region of the hypothalamus. Leptin and CRH increase histamine concentrations, and the stimulation of H_1 receptors in the ventromedial and paraventricular hypothalamic nuclei suppresses feeding. Dr T Sakata (Oita Medical University, Hasama, Oita, Japan) reported data from an H_1 receptor knockout mouse (H_1KO). This mouse did not differ from wild-type in daily food intake, body weight, adiposity or growth. However, H_1KO mice developed obesity more rapidly when loaded with a high-fat diet. Furthermore, H_1KO mice were resistant to the suppressive effects of leptin on feeding.

Dopamine

Dr T Sato (State University of New York Health Science Center, New York, NY, USA) found that the D_2-like receptor antagonist, sulpiride, but not the D_1-like receptor antagonist, Sch-23390 (Schering-Plough Corp), injected into the ventromedial hypothalamus (VMH) increased meal size. Administration of sulpiride into the lateral hypothalamus increased meal number. D_2 receptor mRNA was expressed in the VMH.

Opioids

DAMGO and dynorphin (Neurobiological Technologies Inc) stimulate fat consumption when injected into the hypothalamus of rats according to Dr SF Liebowitz (Rockefeller University, New York, NY, USA). Conversely, rats fed high-fat diets show elevated levels of these opioid peptides in the paraventricular nucleus.

Galanin

Injection of galanin into the hypothalamus produces increased intake of fat and overeating in rats. Rats fed a high-fat diet show elevated levels of galanin in the paraventricular nucleus (PVN), suggesting a positive feedback mechanism underlying overeating of fat. Dr Liebowitz further reported that galanin injected into the PVN increases nucleus accumbens dopamine, implicating galanin in reward.

Nootropics and memory

Oxiracetam

Dr J Wehner (University of Colorado, Boulder, CO, USA) reported that poor-learning DBA/2 mice show decreased γ-calcium-dependent protein kinase (γPKC) in the hippocampus. Administration of the nootropic, oxiracetam (ISF Societa Per Azioni), in these mice enhanced learning and increased PKC in hippocampal membranes.

Pyridostigmine bromide

Dr KD Beck (DVA Medical Center, New Jersey Health Care System, East Orange, NJ USA) suggested that the blood brain barrier may become leaky under stress. The Gulf War troops that took pyridostigmine bromide (PSB), a peripherally-acting anticholinesterase, may have experienced central effects as a result. In Wistar-Kyoto rats, noted for their elevated response to stress, PSB led to an increased response to startle stimuli, an effect not seen in less stress-sensitive Sprague-Dawley rats. Both strains showed reduced central levels of acetylcholinesterase.

σ -Receptor ligands

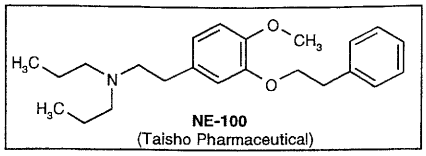
Pregnanolone sulfate

Pregnanolone sulfate (Pharmacia & Upjohn AB; Figure 2), a σ_1 ligand, has been shown to improve memory. Its mechanism of action on Ca^{2+}-signaling appears to be similar to that of (+)-PZT and PRE-084.

NE-100

NE-100 (Taisho Pharmaceutical Co Ltd; Figure 1), a selective σ_1 antagonist, blocked the effects on Ca^{2+} signaling of (+)-PTZ, PRE-084 and PS.

Figure 1.



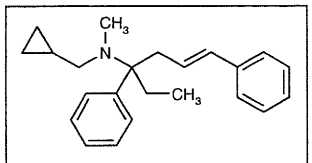
NE-100
(Taisho Pharmaceutical)

Igmesine

Dr G Debonnel (McGill University, Montreal, Quebec, Canada) reported the results of electrophysiological studies of 5-HT neurons in the dorsal raphe and of norepinephrine (NE) neurons. He found that chronic, but not acute, treatment with the selective σ_1 ligand, igmesine (JO-1784; Jouveinal SA; Figure 2) modified the firing pattern of 5-HT, but not NE neurons. This suggests a possible antidepressant action of this compound through an atypical mechanism.

Dr FJ Roman (Institut de Recherche Jouveinal/Parke-Davis, Montpellier, France) reported that igmesine had anti-anxiety and antidepressant effects in several animal models. These actions of igmesine were reversed by pertusis toxin implicating G proteins.

Figure 2.



igmesine
(Jouveinal)

BD-1008 and related compounds

Dr RR Matsumoto (University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA) presented the results of studies of a large number of σ_1 ligands that were derived from the parent compound, BD-1008. Results showed activity of a number of these ligands in tests of cocaine-induced activity and lethality. The potential as of σ_1-receptor ligands as anti-cocaine agents has not been fully recognized.

Summary

The emphasis on feeding seemed to be particularly timely. *Science* (2000) **287** contained a News Focus article entitled, 'Tracing leptin's partners in regulating body weight'. In this article many of the major players were discussed, providing an excellent primer for the papers at the conference. The many new peptides being implicated in feeding are providing a rich resource for the rational development of new therapeutic agents for the treatment of eating disorders.

σ Receptors also seem to have come of age, although the endogenous ligand remains to be discovered. The implication of these receptors in learning and memory, and in disorders including anxiety and depression, point to new targets for treatment strategies that break from the traditional neuromodulators.

Overall, the meeting was a great success, with a wealth of information both about neurochemicals and neuronal mechanisms that would be particularly useful for identifying novel targets for new therapeutics.