Meeting Review

DEPRESSION TO ECSTASY

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The Neuropharmacology of Serotonin
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The objective of this conference on the Neuropharmacology of Serotonin, which was co-chaired and organized by myself and Stephen J. Peroutka (Stanford, CA, USA), was to review and update our current knowledge of serotonin. The neuromodulator serotonin (5-hydroxytryptamine, 5-HT) influences a variety of functions in the central and peripheral nervous systems, including sensory and motor activities. This substance was first reported to occur in the brain in 1953 by Twarog and Page. However, the pharmacology of serotonin substantially predated this, as the effects of the ergot alkaloids, produced by a rye fungus, had been known since 600 BC. This is when the first records appeared describing the hallucinations, pain, and gangrene occurring in people who ate bread made from infected rye. Later this condition was referred to as St. Anthony's Fire. These alkaloids have since become recognized as serotonin antagonists. The neuropharmacology of serotonin was not significantly advanced until the 1980s, when it was found that at least six distinct subtypes of serotonin receptors, belonging to three families, are present in the brain and that these receptors can be acted upon selectively by different pharmacological agents.

Since these findings, much has been learned about serotonin and its mechanisms of action. At this conference in New York, scientists concerned with cellular molecules and mechanisms as well as clinicians interested in the role of serotonin in human behavior and mental illness presented new information on the neuropharmacology of serotonin.

The first session, chaired by George Heninger (New Haven, CT, USA), focused on the anatomy and neurochemistry of the serotonin system. By means of the exciting new technique of three-dimensional reconstruction of serotonin immunostaining, Istvan Tork (Kensington, N.S.W., Australia) mapped the distribution of serotonin nuclei in the human brainstem. This method also permitted a detailed look at the unusual "basket-like" characteristics of some of the serotonin terminals found in forebrain regions and emphasized the extensive distribution of serotonin throughout the brain. Serotonin terminals were shown to make multiple contacts with individual cells, almost completely surrounding the cell like a basket. This work was expanded upon by Laurent Descarries (Montreal, Canada), who presented convincing evidence that not all serotonin is released into a classic synapse; at least half of serotonin's release may be related to a more modulatory or hormonal role of the transmitter.

In view of the expansive distribution and release of serotonin, how then can discrete parts of the serotonergic system be altered pharmacologically? This question was addressed by Jose Palacios (Basel, Switzerland), who observed that while the serotonin terminals all arise from a small group of brainstem nuclei, the distribution of the receptor subtypes in the target regions is complex. For example, 5-HT_{1a} receptors are found in the raphe nucleus and the hippocampus, with some in the neocortex. The 5-HT_{1b} and 5-HT_{1d} receptors, which appear to be largely confined to rat or human brain, respectively, are highly concentrated in the basal ganglia and the substantia nigra. 5-HT_{1c} receptors are concentrated in the choroid plexus, while 5-HT_2 receptors are distributed throughout the neocortex. Further, each receptor subtype has a distinct electrophysiological response (George Aghajanian, New Haven, CT, USA). The 5-HT_{1a} receptor is largely inhibitory (hyperpolarizing) in both raphe nuclei and hippocampus. In contrast, both 5-HT_2 and 5-HT_3 receptors are excitatory (depolarizing). The excitatory effects of the 5-HT_2 receptors may be due to their effects on phosphotidylinositol hydrolysis, while 5-HT_3 receptors may depolarize cells through a direct linkage to an ion channel.

Ray Fuller (Indianapolis, IN, USA) reviewed 15 years of research into the synthesis and characteristics

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of selective serotonin uptake inhibitors, and stressed that these agents block uptake into platelets and astroglial cells as well as into neurons. Non-neuronal sites of action may also play a role in the actions of serotonin uptake inhibitors, which may be clinically useful in treating depression, eating disorders, and perhaps alcoholism.

The second session, which focused on serotonin receptors, was chaired by David Nelson (Tucson, AZ, USA). What emerged from this session was a concise picture of the receptor subtypes, an area where there is much new information. It seems likely that the great diversity of serotonin effects may be due to the differing distribution and pharmacology of the various subtypes of serotonin receptors. In the following summation, I have also included work from researchers who presented in later sessions. Briefly, the serotonin receptor families can be described as follows: (i) The 5-HT_1 family, which consists of the 5-HT_{1a} and 5-$HT_{1b/d}$ receptors; (ii) the 5-HT_2 receptor family, which includes 5-HT_2 and 5-HT_{1c} receptors; and (iii) the 5-HT_3 receptor.

Members of the 5-HT_1 family of receptors have nanomolar affinities for serotonin and for certain ergot alkaloids (Michael Hamon, Paris, France; Derek Middlemiss, Harlow, Essex, UK; Daniel Hoyer, Basel, Switzerland). They are linked to adenylate cyclase, which in some cases causes stimulation of the cyclase and in others results in inhibition (Saul Maayani, New York, NY, USA). Clinically, agonists for the 5-HT_{1a} receptor are useful as anxiolytics and perhaps antidepressants (Duncan Taylor, Wallingford, CT, USA). 5-$HT_{1b/1d}$ receptors are generally negatively coupled to adenylate cyclase and act as terminal autoreceptors; 5-HT_{1d} agonists may have some usefulness in treating migraine headaches, as this receptor subtype appears to be localized to cerebral blood vessels.

The 5-HT_2 and 5-HT_{1c} receptors, which are pharmacologically similar, constitute the 5-HT_2 receptor family. Both are linked to phosphatidylinositol hydrolysis (Elaine Sanders-Bush, Nashville, TN, USA; Paul Hartig, Paramus, NJ, USA) and show an atypical regulation in that they become desensitized in response to antagonists (Josee Leysen, Beerse, Belgium; Sanders-Bush). The ramifications of this are unclear.

The 5-HT_3 receptor appears to be unrelated to either of the previous families as it is linked to an ion channel rather than a guanine-nucleotide binding protein (G protein). 5-HT_3 receptors are localized in limbic regions and the area postrema, where antagonists are postulated to have their effects as anti-emetics (Michael Tyers, Ware, Herts, UK).

The third session, which examined the expression of serotonin function, was chaired by J.P. Green (New York, NY, USA) and provided a summary of the ways in which serotonin activity can be quantified. In addition to studies of the adenylate cyclase and phosphatidylinositol second messenger systems, which were discussed in the previous section, some intriguing results of single-cell recordings in freely moving cats were also presented (Barry Jacobs, Princeton, NJ, USA). These data showed that the firing rates of serotonergic neurons possess an amazing rhythmicity that is altered only by the sleep-wake cycle. Environmental events, physiological challenges, and behavioral alterations do not change the firing rates, implying that the serotonergic system plays a major role in stabilizing brain function. The one exception to this rule is a group of serotonin neurons in the dorsal raphe nucleus that are dramatically stimulated by oral-buccal movements.

The remainder of the session was concerned with the measurements of serotonin function in human subjects. Dennis Murphy (Bethesda, MD, USA) gave a critical evaluation of the peripheral measurements of serotonin. Although platelets have uptake sites and 5-HT_2 receptors similar to brain, these peripheral indices do not necessarily reflect brain function. Cerebrospinal fluid (CSF) measurements, particularly levels of the major serotonin metabolite, 5-HIAA (5-hydroxyindoleacetic acid), appear to more adequately reflect brain function. Serotonin itself occurs at levels too low to be used as a marker. Murphy also introduced the newest, and perhaps most useful, means of determining central serotonin function—the endocrinological challenge tests. These tests essentially consist of administering a serotonergic agent and then determining the blood levels of various anterior pituitary hormones as a measure of serotonin receptor sensitivity (Philip Cowen, Oxford, UK). 5-HT_{1a} receptors increase the release of adrenocorticotropic hormone (ACTH), prolactin, and growth hormone, while 5-HT_2 receptors increase the release of ACTH and prolactin. These tests can then be used to measure central receptor sensitivity in a variety of illnesses.

The final presentation on serotonin measurements in humans was by James Frost (Baltimore, MD, USA) who discussed the use of positron emission tomography (PET) scanning. This technique may allow direct measurement of serotonin receptors or uptake in a living subject. To date, 5-HT_2 receptors have been visualized with ligands such as *N*-methylspiperone and ketanserin, which have a poor ratio of specific to nonspecific binding. However, setoperone and altanserine may achieve higher ratios and thus may represent a major advance. Labeling of the serotonin transporter, principally with N-methylparoxetine, has also been impeded by the lack of agents with sufficiently high specific binding affinities.

The fourth session, chaired by Robert Moore (Stony Brook, NY, USA), focused on a new function for serotonin—its role in the regulation of development and aging. Jean Lauder (Chapel Hill, NC, USA) described the fetal development of the serotonin-neurotransmitter

system and advanced the concept that serotonin receptors may play a role in development. In support of this, the binding of serotonin to the 5-HT_{1a} receptor causes brain astroglial cells to release a growth factor that regulates the development of the serotonergic neuron (Whitaker-Azmitia). Moreover, the levels of this subtype of receptor peak during key phases of development and may subsequently be downregulated as the astroglial cell matures. George Anderson (New Haven, CT, USA) summarized the current findings of increased serotonin levels in childhood autism. Since, as described by the previous speakers, serotonin regulates brain development, this work is of particular interest.

Moving from development to the adult animal, Efrain Azmitia (New York, NY, USA) discussed the concept of adult plasticity—that is, the brain is not constant even in adulthood. At least for the brain's serotonin system, regrowth after damage is possible. Azmitia also raised the exciting possibility that some of the factors involved in regrowth of the serotonin system, such as laminin, S-100, and several ACTH analogs, may be the same as those regulating brain development.

The final three speakers of this session focused on aging. Cornelius Vanderwolf (London, Ont., Canada) and Alan Cross (London, UK) emphasized that both serotonergic and cholinergic deficits may occur in dementias, and that the decrease in serotonin activity may in fact be a necessary component. Harry Steinbusch (Amsterdam, The Netherlands) discussed the morphological differences in serotonin terminals in aged rats. In these animals, serotonin terminals have an aberrant appearance and are reduced in number. When serotonin neurons from fetal rats are transplanted into young or aged animals, the fiber outgrowth from the transplant does equally well in rats of both ages. In fact, it appeared that the presence of fetal tissue may actually reverse the terminal changes seen in aged animals. This could be interpreted as indicating that the aging process is related not to the presence of a toxic substance, but rather to the lack of a trophic substance. It is interesting to speculate that this factor may be the same as the substance that regulates development and plasticity.

The fifth and sixth sessions, chaired by Hermann Van Praag (Bronx, NY, USA) and Max Fink (Stony Brook, NY, USA), respectively, examined the role that serotonin may play in human mental illnesses. The sessions included animal studies relevant to human disease as well as clinical studies. Anat Biegon (Rehovot, Israel) focused on the mechanisms by which steroids may interact with serotonin receptors and induce depressive symptoms. Both estrogens and the stress-related hormone corticosterone can alter the number of serotonin receptors expressed, and this may explain the role of stress and gender in depression. Sexual behavior is also often altered in depression, and Boris Gorzalka (Vancouver, B.C., Canada) presented evidence that serotonin is the major neurotransmitter that influences sexual activity in animal models.

In discussing the role of 5-HT_2 receptors in sleep, A. Wauquier (Leiden, The Netherlands) suggested that these receptors release an as yet unknown hypogenic factor that is responsible for slow-wave sleep. 5-HT_1 receptors do not appear to play a major role. Alan Frazer (Philadelphia, PA, USA) discussed animal studies, in which the sensitivity (but not the number) of both 5-HT_1 and 5-HT_2 receptors is likely to be involved in causing different aspects of depression. These observations suggest that manipulation of these receptors with pharmacological agents may be useful in treating some forms of depression.

Herbert Meltzer (Cleveland, OH, USA) and J. John Mann (New York, NY, USA) presented clinical studies that show a role for serotonin in depression. In some cases of depression, serotonin activity is diminished, possibly because of a decrease in terminal density. One particular aspect of depression that may reflect reduced serotonin activity is the inability to control some impulsive behaviors, such as suicide and aggression. The relation of these findings to obsessive-compulsive disorders (OCD) was addressed by Thomas Insel (Bethesda, MD, USA). Some cases of OCD may be related to an increase in CSF 5-HIAA, yet the symptoms often respond to serotonin uptake inhibitors. Such apparently incongruous results may reflect the fact that only discrete regions of the brain are altered in any particular mental illness and thus CSF levels alone cannot always be predictive.

In addition to depression, serotonin has long been implicated in eating disorders, pain, and migraine. In animal studies on eating behaviors, 5-HT_{1a} receptor agonists resulted in increased feeding, while 5-HT_{1b} receptor agonists caused decreased feeding (Gerald Curzon, London, UK). The 5-HT_{1b} receptor agonist effects were most pronounced in female rats, which may explain the gender differences observed in human eating disorders. David Jimerson (Boston, MA, USA) discussed his clinical findings, which suggest that abnormal serotonin transmission occurs in patients with eating disorders, particularly those with bulimia-associated binge eating. These disorders are thought to be associated with decreased serotonin activity.

The role of serotonin in pain is complex (Brian Richardson, Basel, Switzerland). It appears that serotonin can be either algesic (pain-producing) or analgesic, depending on the point in the nervous system at which it is released. Recently, significant advances have been made in the treatment of migraine with selective 5-HT_{1d} receptor agonists, such as sumatriptan. However, as discussed by Patrick Humphrey (Ware, Herts, UK), migraines appear to be a vascular event. Since serotonin is known to influence vascular and other smooth muscle responses, the effect of 5-HT_{1d} receptor

agonists on migraine does not necessarily imply that they will ease other types of pain.

The final session of the meeting, on MDMA (methylenedioxymethamphetamine) and related compounds, was chaired by Lewis Seiden (Chicago, IL, USA) and generated the most controversy of any of the meeting's sessions. The amphetamine-related psychotogens characterized by MDMA (Ecstasy) are novel psychotropic agents that have mind- and mood-altering properties without being hallucinogenic. In discussions on the mechanism of action of MDMA, it was hypothesized that this agent releases serotonin, which then acts on postsynaptic 5-HT_{1b} receptors; 5-HT_2 receptors, which are often involved in hallucinogen action, appear not to be involved (David Nichols, West Lafayette, IN, USA; Milt Titeler, Albany, NY, USA). The controversy generated by this session centered on whether or not MDMA and related agents, such as *p*-chloroamphetamine and fenfluramine, have neurotoxic properties. James Gibb (Salt Lake City, UT, USA) and Christopher Schmidt (Cincinnati, OH, USA) argued that these agents are neurotoxic, possibly through production of a reactive metabolite of dopamine. In other studies based on radiolabeled ligand binding and morphological assessments, both Mark Molliver (Baltimore, MD, USA) and Errol DeSouza (Baltimore, MD, USA) agreed that the toxicity was dose dependent and occurred in both rats and primates. However, regeneration was observed in rats 2 to 12 months after exposure. In the final presentation, George Ricaurte (Baltimore, MD, USA) provided dramatic evidence that a serious level of damage had occurred to the serotonin neurons of 34 human MDMA users. The general discussion of this session centered on how to interpret these findings, and whether or not true toxicity did occur, particularly regarding the agent fenfluramine which has been used clinically as an appetite suppressor for several years with apparently few untoward effects. Although this issue was not resolved, all agreed that a specialized meeting on serotonin neurotoxicity was needed. Such a meeting was last held in 1978, also under the auspices of the New York Academy of Sciences.

In summary, this meeting left most of the participants with the sense that a great amount of progress has been made in serotonin research. With the advances made by basic research and clinical studies, it now appears that our knowledge of the serotonergic system will enable us to manipulate it in many more ways than was previously thought possible. However, it was generally agreed that this field was expanding so rapidly that all of the participants would have to meet again in the near future.