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General Editors: J. TUOMISTO & M. K. PAASONEN

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NEUROTRANSMISSION

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LIISA AHTEE

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Volume 1: Receptors and Cellular Pharmacology
Volume 2: Neurotransmission
Volume 3: CNS and Behavioural Pharmacology
Volume 4: Drug Therapy
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Volume 6: Mechanisms of Toxicity and Metabolism

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Preface

The International Union of Pharmacology (IUPHAR) held the Sixth International Congress of Pharmacology in Helsinki, Finland on 20–25 July 1975. The scientific programme was organised with the help of the International and Scandinavian Advisory Boards and it consisted of 15 invited lectures, 20 symposia, 5 seminars on methods, and volunteer papers, some of them as poster demonstrations. Altogether 1580 communications were delivered by the 2 600 active participants attending the Congress.

The texts of the invited lectures and symposia have been included in the Proceedings of the Congress. It is readily noticeable that all the major areas of pharmacology, including clinical pharmacology and toxicology, are well represented. Special attention has been paid to several interdisciplinary areas which are on the frontiers of pharmacology and have connections with physiology, biochemistry and endocrinology. Many of the topics are of special interest to internists, psychiatrists, neurologists and anaesthesiologists. Chapters on the abuse of alcohol, new teaching methods and the conservation of wild animals reflect the wide scope of the Congress.

One can hardly imagine any other Congress Proceedings where more world-famous authors representing pharmacology and the related sciences have reported the most recent developments in their special fields. The invited lectures give a particularly clear introductions to the areas in question, even for those previously unfamiliar with them.

For the first time the Proceedings of an International Pharmacology Congress have been produced by the photo offset-litho process. This method was chosen in order to publish the volumes in the shortest possible time. It clearly demands the emphasis be placed upon the scientific content of the volumes, possibly at the expense of retaining some infelicities of style or presentation.

We are convinced that these Proceedings present a unique opportunity to keep abreast of the latest developments in pharmacology and related areas of research. Our sincere thanks are due to the authors, the members of the advisory boards and our colleagues of the Programme Committee for making the scientific programme of the Congress so successful and the publication of the Proceedings possible.

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Contents

Invited lectures

Tryptaminergic neurotransmission.

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General properties of tryptaminergic neurons

The term tryptamine receptor was introduced by Gaddum (27) for tissue sites responding to 5-hydroxytryptamine (5-HT) because of the similarity of the actions of tryptamine and its 5-hydroxy-derivative on peripheral organs. As there is no evidence for a transmitter role of tryptamine in the mammalian brain, I shall, for brevity's sake, use the term tryptaminergic neuron for those cerebral pathways which contain 5-hydroxytryptamine and release it on stimulation. This does not imply that exogenous tryptamine and 5-hydroxytryptamine necessarily act on the same receptors and always produce the same effect. In the fowl, for example, intra-ventricular injection of tryptamine causes arousal, and 5-HT injected by the same route sends the chick to sleep (48). Neither does it preclude the possibility that a small number of tryptaminergic neurons contain an indole which is closely related to, but not identical with, 5-HT (38).

That neurons which contain 5-HT also release it, is often taken for granted. However, direct evidence of release has been obtained, for example by perfusing a lateral or the third ventricle of a cat's brain with artificial cerebrospinal fluid and demonstrating the appearance of 5-HT in the perfusate when the two most rostral raphe nuclei were stimulated electrically (36, 8).

The tryptaminergic neurons have their cells of origin in the raphe nuclei of midbrain and anterior medulla. Their axons are sent caudally into the cord and rostrally into all regions of the brain. However, there are great differences in the density of terminals which, incidentally, can be assessed not only histologically but by measuring, in the particular part of the brain, either the concentration of 5-HT, that of tryptophan hydroxylase or the uptake of [^{3}H] -5-HT. Most of the cerebellum contains but little 5-HT, while terminals are dense in the suprachiasmatic nucleus, the superior colliculi and parts of the septum. Yet, Hökfelt (35), using rat brain, calculated that even in the suprachiasmatic nucleus only 1 in 20 of all boutons appeared to contain 5-HT, and in the cortex this proportion falls to 1 : 1500 as estimated by autoradiography (46). From these findings one must expect many cerebral functions to be influenced by tryptaminergic

neurons, and also the effects to be determined by the function of the neurons onto which the tryptaminergic axons impinge.

A question which is often asked is whether 5-HT polarizes or depolarizes, in other words, inhibits or stimulates nerve cells. There is apparently no general answer to that question. In invertebrate ganglia such as the buccal ganglia of Aplysia, no fewer than 6 different responses were obtained by iontophoretic application of 5-HT (28). A fast and a slow depolarization, and a fast and a slow polarization, were associated with increased conductance to different ions (Na^+, K^+, Cl^-); two further effects were accompanied by a decrease in ion permeability. Since the cells of the buccal ganglion are innervated by two 5-HT releasing neurons originating in the cerebral ganglion, one must assume that the neurons make contact with six different receptors. There is no evidence that the situation is equally complicated in the mammalian brain. However, it has been shown by Aghajanian and Haigler (1) that cells with a heavy tryptaminergic input respond to exogenous 5-HT with inhibition, whereas cells with little or no such input are frequently excited by 5-HT, as also reported earlier by Boakes et al. (12) for cells of the lower brain stem. It will be shown later that 5-HT neurons are sometimes in series with GABA containing neurons, so that the end effect of depolarization would be inhibition, and of hyperpolarization excitation.

The ganglia of Auerbach's plexus have frequently been used as a model for drug actions on the brain. Recently, Henderson and North (33) recorded intracellularly from cells of this plexus which were depolarized by focal electrical stimulation. This gave rise to an excitatory postsynaptic potential (e.p.s.p.) which must have been produced by the liberation of A.Ch. Local application of 5-HT depressed the e.p.s.p., thus indicating that 5-HT had reduced the release of A.Ch. It is possible, but cannot be taken for granted, that a similar effect is produced whenever 5-HT is released in the brain at terminals making contact with cholinergic neurons. In fact, experiments to be discussed later (52) suggest stimulation rather than reduction of cholinergic activity in the hypothalamus after local injection of 5-HT.

Before discussing my main subject, the possible functional role of certain tryptaminergic pathways, a word of caution is required about attempts at correlating 5-HT concentration and turnover in the brain with functional activity of the neurons. Whatever correlation exists is not simple; this is shown by the fact that increased availability of 5-HT, for example by feeding tryptophan, does not by itself cause abnormal function, and may simply lead to increased metabolism of 5-HT (30).

Homeostasis; autonomic functions

1. Sleep. It is probably no accident that 5-HT content and turnover in the brain show strong circadian rhythms (60); 5-HT containing neurons are involved in a number of homeostatic mechanisms and autonomic functions which are also affected by the time of day. The first phenomenon shown to depend on the integrity

of tryptaminergic neurons was sleep. Jouvet in 1962 (39), and his co-worker Renault (57) discovered that cats given p-chlorophenylalanine (pCPA) became insomniac. Both slow wave and paradoxical sleep were affected, and the effect could be reversed by the administration of 5-hydroxytryptophan. The action of pCPA could be mimicked by destroying the raphe nuclei of midbrain and pons.

2. Temperature regulation. In 1964 Feldberg and Myers (25) pointed out that cerebral 5-HT appears to be involved in temperature regulation. They found that injection of 5-HT into the hypothalamus raises the temperature in the cat. Myers et al. (51) showed that 5-HT is released from the hypothalamus when an animal is cooled: they implanted a 'push-pull cannula' into the hypothalamus of a monkey and tested the effluent for 5-HT; when the animal was subjected to a blast of cold air, the 5-HT content of the perfusate rose by a factor ranging from 2 to 24. Myers and Waller (52) obtained evidence suggesting that the released 5-HT activated cholinergic pathways involved in heat production. Harvey and Milton (32) have observed that the fever produced in a cat by bacterial pyrogen, or by intracerebro-ventricular injection of prostaglandin E_1, is much reduced after the administration of pCPA. It thus appears that, in the absence of tryptaminergic neurons, the cat has difficulties in raising its body temperature. However, there are puzzling species differences in the role of 5-HT in temperature control. Thus Bligh et al. (11) found that injection of 5-HT into the lateral ventricle of sheep, goats and rabbits activated mechanisms of heat loss, not of heat production or preservation.

In view of the participation of 5-HT containing neurons in temperature and sleep regulation, it might be expected that they also play a role in hibernation. Inhibition of 5-HT synthesis in the ground squirrel by pCPA prevents hibernation, and raphe lesions inhibit it either partially or completely (66). There has been no analysis of the multiple mechanisms involved.

3. Respiration. Many experimenters will have come across the difficulty of respiratory depression when anaesthetizing a cat treated with an inhibitor of monoamine oxidase. The phenomenon appears to be due to the accumulation of 5-HT, since it can also be produced by 5-hydroxytryptophan, and since the latter is inactive in the presence of an inhibitor of DOPA decarboxylase injected cerebroventricularly (5). This effect may be an example, of which more will follow later, of the prevention by tryptaminergic neurons of excessive responses to sensory stimuli, CO_2 being the stimulus active in controlling respiration.

4. Vasomotor reflexes. Stimulation of the nucleus raphe obscurus causes a fall in blood pressure and a reduction of spontaneous and evoked sympathetic activity recorded from the white rami communicantes; this reduction is mimicked by an intravenous injection of 5-HTP (54). The pathway involved has its terminals on cells of the intermedio-lateral columns.

Release of pituitary hormones

There is evidence for an inhibitory effect of 5-HT, and therefore probably of tryptaminergic neurons, on the liberation of a number of hypothalamic releasing or release-inhibiting factors. The demonstration of 5-HT and tryptaminergic terminals in the median eminence (58, 18) shows a possible morphological basis for such a function. As a result of administering 5-HT, the appearance in the blood stream of pituitary hormones is either increased or decreased, depending on whether their secretion is mainly controlled by a hypothalamic polypeptide which furthers, or by one which inhibits, secretion. Thus it has been shown that secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) are suppressed, and of melanophore stimulating hormone (MSH) and prolactin (P) enhanced, by injection of 5-HT into the third ventricle or by administration of 5-HTP; the opposite effects follow treatment with pCPA (45, 61, 40, 41, 44, 68, 19, 20). The explanation is, of course, that LH and FSH secretion take place in response to liberation of releasing factors, whereas secretion of MSH and P is mainly controlled by hypothalamic inhibitory factors (PIF and MSH-R-IF). There is some evidence, although the subject is still under discussion, that the releasing factors for corticotrophin (72) and thyrotrophin (70) are also under the inhibitory influence of tryptaminergic neurons.

The arrest in the liberation of LH releasing factor by 5-HT was visualized by a fluorescent antibody reaction in the guinea-pig brain (47). After intraventricular injection of 5-HT, sections of the preoptic and suprachiasmatic nuclei of the hypothalamus reacted with an antiserum to the releasing factor, thus producing fluorescent cells absent from the controls. The interpretation is that, when secretion of the releasing factor stops, it accumulates in the cells which manufacture it.

To complete the picture, it should be added that an inhibitory effect of 5-HT and 5-HTP has been observed on oxytocin release in the suckling rat (50). The exact site of this action is not yet known. It is interesting that secretion of oxytocin and of prolactin are influenced by 5-HT in opposite directions.

The work of Taleisnik *et al.* (68) has greatly helped in our understanding of the complicated circuitry involved in the action of tryptaminergic neurons in the control of secretion of MSH and prolactin from the anterior lobe of the rat. A number of stimuli, for example intravenous injection of hypertonic saline, cause secretion of MSH, an effect explained by reduced release of the inhibitory factor MSH-R-IF. Not only the injection of 5-HT into the third ventricle, but also that of γ-aminobutyric acid (GABA), causes MSH release; both effects are prevented by picrotoxin, a known GABA antagonist. The hypertonic saline-induced MSH secretion can also be blocked by picrotoxin, pCPA and methysergide. The effect of picrotoxin suggests that GABA containing neurons are involved, and that of pCPA and methysergide point to a role of tryptaminergic neurons in this reduction of release of MSH-R-IF which leads to MSH secretion.