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# Clinical Pharmacology of Serotonin

Volume Editors

F. Sicuteri, Florence, and E. Schönbaum, Oss

Proceedings of the Satellite Symposium on the Clinical Pharmacology of Serotonin,
Helsinki, July 26–27 1975

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# Preface

In Helsinki, on July 26 and 27, 1975, a number of people gathered at a Satellite Symposium of the 6th International Congress of Pharmacology to discuss various aspects of the role of serotonin as a neurohumor in health and disease.[1] Presentations covered a wide range of topics and the good attendance even at the last paper encouraged our belief that the meeting was both relevant and timely. We are most grateful to Prof. *P. Peltola* of the University of Helsinki for his excellent local organization and to Dr. *Bruno Anselmi* and Dr. *Pierluigi Del Bianco* of the Department of Clinical Pharmacology, University of Florence, for their participation in preparing the programme. Hoffmann-La Roche Ltd., Basle; Sandoz Ltd., Basle and UCM-DIFME, Turin assisted the organizers by means of a grant that supported part of the secretarial and printing expenses as well as some local costs. Dr. *Thomas Karger,* of S. Karger AG, Basle, has kindly agreed to publish this volume which is largely, but not completely, based on the papers presented. Mr. *R. Steinebrunner* has rendered invaluable assistance with matters related to getting the book on its way as quickly as possible. Finally, we wish to acknowledge Miss *Monique van der Borg,* Oss, Mrs. *Mara Masi Saccenti* and Miss *Joan Nonenbacher,* Florence, for their devoted and cheerful secretarial help.

*F.Sicuteri* *E. Schönbaum*

[1] Abstracts of this symposium have been published in Agents and Actions *5:* 484–507 (1975).

# Contents

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# Why Clinical Pharmacology of Serotonin?

*F. Sicuteri and E. Schönbaum*

Department of Clinical Pharmacology, University of Florence, Florence, and Department of Pharmacology, Scientific Development Group, Organon International BV, Oss

Serotonin (5-hydroxytryptamine, 5-HT) has been a friend of pharmacologists for many years. Depending on the investigators' interests, it was studied in the salivary glands of the octopus, in the mammalian intestine, in serum during blood clotting, or in venom of scorpion or wasp. It was known as enteramine, vasotonin, vasoconstrictine but nowadays usually one talks about serotonin (5-HT). In textbooks of pharmacology it has a somewhat vague place: local hormones, control of pain, autacoids are some headings under which histamine and antihistamines and/or 5-HT and 5-HT antagonists are discussed. The role of 5-HT in the central nervous system (CNS) is usually considered secondary to its presumed association with a wide variety of marketed and experimental psychotropic or psychotogenic drugs. Experimental preclinical research on 5-HT proceeds, broadly speaking, in the areas of CNS biology – from single unit recording studies to behavioral observations in spiders or primates – in smooth muscle and receptor pharmacology, and in those fields of study where platelets are of importance. There have been excellent recent reviews of all these fields (5, 6, 9). The purpose of this volume is to add some recent results obtained from studies in man. Moreover, several contributions touch upon the critical problems encountered when decisions need to be taken with respect to early human investigation. The editors certainly do not intend this volume as a comprehensive review. Papers cover selected, specific areas and are a contribution to the constructive discussion that leads to improvements of therapy.

The high content of 5-HT of human and most animal platelets or thrombocytes has stimulated much research. While nobody doubts that platelet 5-HT fulfils a useful hemostatic role, platelets themselves survive equally well when depleted of 5-HT (15). Platelets undoubtedly carry some 'pump' for 5-HT, as the concentration gradient towards plasma is $10^3$ or more. No wonder that platelets have been used as models for the study of 5-HT and 5-HT-related drug inter-

actions. Some investigators consider the platelet as a convenient model for serotonergic neurons. It might perhaps be useful for the prediction of the CNS activity of certain drugs (23, 24). Others feel that platelet aggregation induced by 5-HT is useful for the study of certain aspects of hemostasis, thrombosis and of drugs expected to have antithrombogenic effects (15). In such studies, the importance of species differences and the problem of applicability of animal data to man cannot be overemphasized.

Human and rabbit platelets differ considerably with respect to aggregability *in vitro* by 5-HT. Most drugs known to be 'specific' peripheral (i.e. smooth muscle) 5-HT antagonists appear to inhibit 5-HT-induced platelet aggregation (16) at concentrations at which they also may interact with 5-HT in the CNS. Clearly, there are limitations to the validity of information gained from platelets with respect to the CNS situation.

Platelets, however, do not only release 5-HT. They also release prostaglandins (and therefore thromboxanes!) and other biologically active materials (12, 14, 27). Prostaglandin cyclic endoperoxide $H_2$ (4, 17), e.g., aggregates platelets and contracts swine coronary arteries *in vitro* (8). In the presence of 5-HT, the endoperoxide causes much stronger contractions (8). This observation not only suggests the possibility of increased resistance in coronary arteries with areas of endothelial damage, but it points to a possible mechanism for vascular pathologies such as pulmonary hypertension, essential headaches, etc.

There is considerable evidence in favor of involvement of 5-HT in migraine and other essential headaches (22). There are other theories in which emphasis is placed on enzymatic defects (19), histamine, or unusual vasoactive materials.

As essential consideration in all these hypotheses should be that there is more than one type of 5-HT receptor (7). Several peripheral 5-HT receptors have been postulated, e.g. D and M receptors, blocked by phenoxybenzamine and morphine, respectively. This distinction, however, based largely on smooth muscle studies, is not satisfactory (26). Moreover, effects seen in peripheral 5-HT-sensitive systems do not necessarily permit conclusions or even speculation about 'receptors' in the CNS. The function of 5-HT in the CNS has not yet been clarified. The effect produced in the CNS by 5-HT or by drugs structurally related to 5-HT will depend on the final balance of drug distribution, type and condition of synapses, inhibition or block of excitatory or inhibitory cells and background activity from all cells. The difficulties encountered in such an analysis are illustrated by *Van Riezen et al.* (p. 37) in a study of ponto-geniculo-occipital spikes. Yet, this kind of analysis is essential for the pharmacological characterization of potentially clinically useful substances. *Van Riezen*'s paper illustrates the point that a substance proven to be a peripheral 5-HT antagonist (25) may act differently in the CNS. Moreover, in one particular vascular bed, a number of drugs have shown partial agonist characteristics (21). In 1953,

*Gaddum* observed, and this has since then been confirmed many times, that lysergic acid diethylamide (LSD) is an antagonist of 5-HT on smooth muscle. It is surprising that the proven 5-HT-agonistic action of LSD on one type of positively identified tryptaminoceptive (postsynaptic) neuron (7) and its lack of activity on other types of neurons in the mammalian CNS has not found more emphasis outside the specialized neuroscience literature. The antagonist-agonist behavior of LSD described above is shared by other substances which also show peripheral 5-HT antagonism (21).

Tryptaminergic neurons are involved not only in temperature regulation (13, 20), food intake (3), neuroendocrine control (5, 6, 18), and extrapyramidal activity, but also in more complex functions such as sleep, mood, perception, including pain (7), and sexual behavior (18). The potential usefulness of drugs intended to normalize such function can only be established in man: clinical (human) pharmacological investigations fulfil this task.

Drugs modifying 5-HT, and also noradrenaline, dopamine or acetylcholine, in appropriate areas of the brain, are involved in the control of sleep. Many of these studies have been done with cats. However, drug effects are notoriously species-dependent so that observations in the cat do not necessarily apply to man, and differences may be of a qualitative or quantitative nature. One particular aspect of the importance of 5-HT in sleep has been reviewed at this symposium by *Hartman* (p. 26) who has discussed the effect of the 5-HT precursor *L*-tryptophan.

The role of 5-HT in the control of the complex function called 'mood' has been the subject of thousands of pages of research reports. At the Helsinki symposium on the clinical pharmacology of 5-HT, several papers dealt with effects of oral tryptophan or, conversely, of tryptophan-deficient diets. Data concerning the concentration of endogenous tryptophan in the plasma and cerebrospinal fluid of depressive patients were also presented. As the synthesis of 5-HT in brain is partly dependent on the plasma level of free (unbound) tryptophan (11), the dietary control of tryptophan is one of the few direct approaches to the manipulation of 5-HT in man and therefore a welcome experimental tool. Unfortunately, there is so far no convincing evidence that control of dietary tryptophan can exert predictable changes of mood in normal subjects. However, the effect of dietary manipulation on mood in depressive subjects has not yet been systematically investigated. The above reasoning implies the expectation that depression (or schizophrenia or other pathological mood changes) are associated causally with 5-HT abnormalities. This assumption remains to be proven. An even more tenuous belief is that drugs effective against depressive disorders act by increasing the availability of more 5-HT or catecholamines at appropriate receptor sites in the brain.

5-HT has a long history of involvement with inflammation and pain. Research into the peripheral aspects of pain has turned more recently to kinins,

prostaglandins and thromboxanes and other mediators. In the CNS aspects of pain, 5-HT undoubtedly plays an important role, but even in the more limited field of essential headache, including migraine, the significance of 5-HT remains to be clearly defined. Some 15 years ago, *Sicuteri* hypothesized that 5-HT is somehow related to essential headache. More recently, *Sicuteri* formulated the idea that a biochemical lesion associated with 5-HT metabolism may lead to pain by causing insufficient inhibition of cerebral pain assimilation. *Sicuteri* (22) believes that essential headache may be the most common example of a functional biochemical disruption of central pain modulation. Based on recent evidence, *Sicuteri* sees an association between the use of tryptophan or 5-hydroxytryptophan, perhaps together with benserazide (p. 46), and the use of conventional anti-migraine drugs which although they are peripheral 5-HT antagonists they may well function as 'proserotonin' agents. *Kangasniemi* (p. 60) found that 5-hydroxyindoleacetic acid in cerebrospinal fluid was increased in patients whose headache was relieved by 5-HT antagonists, a finding that supports *Sicuteri*'s hypothesis. *Anthony* (1) has concluded that 5-HT has a tonic (constrictive) influence on human and animal blood vessels. Due to a release of 5-HT that is specific for migraine (it is not observed during stress or nonmigrainous headaches) less 5-HT may be available and reduction of vascular tone occurs and, as a consequence of this, vasodilation, particularly of the external carotid circulation. The release of 5-HT during migraine, is due to a plasma factor which appears in the blood during the attack (1). Although reserpine is known to precipitate migraine attacks, no differences between migrainous patients and controls were found with respect to the effect of reserpine on blood platelet 5-HT (10) or plasma 5-HT (1).

Neuroendocrine control in its broadest sense, including, for example, temperature regulation, sexual and other rhythms, and appetite involves 5-HT. The classical papers on species differences with respect to the effect of 5-HT on thermoregulation have been reviewed elsewhere (13, 20) and so has the control of biological rhythm by the pineal gland through melatonin (2). Appetite has been drawn into the field of 5-HT studies because of the weight gain produced by certain drugs interacting with 5-HT, and because a number of appetite suppressants also can modify 5-HT metabolism. Nevertheless, the role of 5-HT in controlling food intake is not understood, and the more complex problem of appetite even less so.

The importance of 5-HT in the control of sexual behavior has been generally recognized since *Gessa*'s experiments with parachlorophenylalanine (18). Human data are controversial. Sexual deviations are unaffected by treatment with parachlorophenylalanine alone or with testosterone (p. 88) or, on the other hand, with 5-hydroxytryptophan alone or in combination with benserazide (p. 90). Other studies, however, described beneficial effects of tryptophan (p. 96), parachlorophenylalanine (p. 97) and other drugs. The different results can be related

to the particular type of patient, e.g. headache sufferer, and his particular pattern of 5-HT metabolism.

Interesting studies have been carried out in other areas of CNS disease, e.g. myoclonus. Treatment with *L*-5-hydroxytryptophan, in combination with carbidopa, appears effective (p. 71).

Some comments should be made about the metabolic pathways of *L*-tryptophan (p. 129). Tryptophan can be metabolized via 5-hydroxylation to 5-hydroxyindoleacetic acid, but it can also be broken down to niacin. Leaving aside the problems related to nutritional deficiencies, the metabolism via 5-hydroxylation and decarboxylation to 5-HT and its oxidation are of prime interest to clinical pharmacologists: the activity of monoamine oxidase (MAO) determines in part the activity of 5-HT. However, MAO is not specific for 5-HT: other monoamines are also oxidized by this enzyme which occurs in several isoenzymatic forms. MAO activity changes in various clinical conditions, but the question of the significance of changes of one particular type of MAO, e.g. platelet MAO (19), remains. In human studies, platelets and cerebrospinal fluid appear to be the only means for the evaluation of 5-HT changes. The considerable technical difficulties encountered with studies of platelet MAO have given rise to the development of various tests; *Anselmi et al.* (p. 115) have observed that a single oral dose of 25 mg of pargyline so strongly suppresses platelet MAO that a test for MAO resynthesis (p. 115, 124) could be developed. Platelet MAO is abnormal in a variety of conditions, including, e.g., arterial hypertension (p. 115) or carcinoid (p. 81).

This brief, incomplete, personal, and very biased reply to the question 'Why clinical pharmacology of serotonin?' will interest some colleagues and alienate others. If it arouses sufficient interest so that the reader proceeds to the following pages, then there is hope that our effort to contribute to the study in man of the role of 5-HT in health and disease will have been worthwhile.

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Prof. *F. Sicuteri,* Department of Clinical Pharmacology, University of Florence, *I–50134 Firenze* (Italy)

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# Serotonergic Functions in Man

*T.N. Chase, I. Shoulson and A.C. Carter*

Laboratory of Neuropharmacology, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Md., and Downstate Medical Center, Brooklyn N.Y.

## *Introduction*

Considerable experimental effort continues to be directed towards the elucidation of the relationship in man between the activity of identifiable neurohumoral systems and specific centrally-mediated functions. Preclinical studies during the past decade have provided evidence linking the activity of serotonin (5-HT) containing neural pathways to such diverse functions as sleep, pain perception, sexual behavior, extrapyramidal function, seizure thresholds and neuroendocrinologic regulation (7). Although these investigations have at times failed to produce convincing results in the experimental animal, clinical approaches to this problem have yielded even less certain evidence favoring a contribution of central serotonergic systems to the regulation of any human function. This situation, which contrasts with a relative success of both clinical and preclinical studies of the dopamine system, may in part reflect methodological inadequacies. It is also possible, however, that this situation arises as a consequence of the essential functional characteristics of the 5-HT system in man.

Both biochemical and pharmacologic strategies have been applied to studies of the relationship between serotonergic mechanisms and centrally-mediated functions in man. With respect to the former approach, attempts have been made to correlate levels of 5-HT and of its principle metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in various body tissues and fluids to specific clinical signs of central nervous system dysfunction. The pharmacologic approach depends upon clinical observations during the administration of drugs having relatively selective effects on synaptic activity mediated by 5-HT. Both approaches are relatively indirect and beset by methodological difficulties. Used together, however, they may often provide important clues relevant to the operation of the 5-HT system.

## *Extrapyramidal Function*

### *Biochemical Studies*

Numerous preclinical studies in various mammalian species suggest a relationship between serotonergic activity and extrapyramidal function (7). Moreover, direct measurements in postmortem specimens of brain from parkinsonian patients have disclosed substantially reduced 5-HT concentrations (14). Thus it is not surprising that steady-state concentrations of 5-HIAA tend to be diminished in the spinal fluid of individuals with Parkinson's disease (6). Furthermore, central 5-HT turnover, as estimated by the oral probenecid loading technique (8), also appears to be reduced in patients with Parkinson's disease or Guamanian parkinsonism-dementia (fig. 1). Similar changes have not, however, been found in patients with such other extrapyramidal disorders as Huntington's chorea or torsion dystonia (fig. 1). Despite the uncertainties of using lumbar spinal fluid levels of 5-HIAA, with or without probenecid loading, to evaluate the functional state of central 5-HT systems in man, the foregoing results might be taken to indicate that hypofunction of serotonergic pathways contributes to the appearance of parkinsonian signs.

### *Pharmacologic Studies*

Further evaluation of this possibility derives from pharmacologic studies (table I). It is well known that parkinsonian signs can be induced or exacerbated

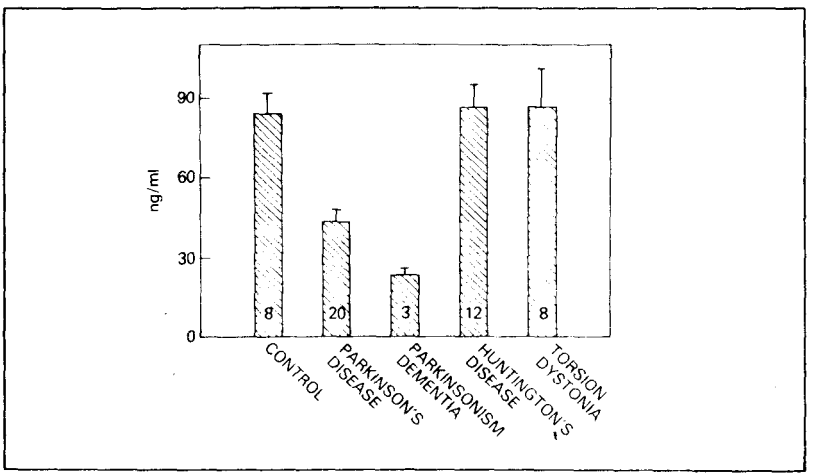


*Fig. 1.* Central 5-HT turnover as estimated by the probenecid-induced accumulation of 5-HIAA in lumbar spinal fluid in patients with various extrapyramidal disorders and in control subjects. The number of individuals studied is given at the base of each bar.

*Table I.* Effect of drugs acting on serotonergic mechanisms in patients with extrapyramidal disease[1]

| | Parkinson's disease | Huntington's chorea |
|---|---|---|
| Reserpine or tetrabenazine | induce or exacerbate | ameliorate |
| *p*-Chlorophenylalanine | none | none |
| *L*-5-Hydroxytryptophan | exacerbate[2] | exacerbate |
| *L*-Tryptophan | none | none |
| *L*-Tryptophan plus pyridoxine | exacerbate | none |
| Fenfluramine | unknown | none |

[1] Literature references given in text.
[2] In combination with a peripheral decarboxylase inhibitor (Carbidopa).

by reserpine or tetrabenazine. On the other hand, these agents tend to ameliorate choreatic movements in patients with Huntington's disease (12). Since reserpine and tetrabenazine interfere with catecholaminergic synaptic function as well as with that mediated by 5-HT, observations in patients receiving drugs which act more selectively on central monoaminergic systems are needed. In this regard studies using α-methylparatyrosine warrant consideration. The administration of this relatively specific inhibitor of catecholamine synthesis affects parkinsonian and choreatic patients in the same manner as reserpine or tetrabenazine (4, 5), thus suggesting that alterations in dopaminergic or noradrenergic systems might account for the extrapyramidal effects of reserpine-like agents.

Drugs acting relatively specifically on 5-HT-mediated synaptic function should, in theory, provide more definitive evidence for or against the participation of serotonergic systems in the regulation of human extrapyramidal function. One such drug, parachlorophenylalanine, a potent inhibitor of 5-HT synthesis, has been given orally in daily doses of up to 4 g to patients with either Parkinson's or Huntington's disease (3, 11). No significant alteration in motor function was observed in either patient group. Since the dose levels used were sufficient to substantially depress the CSF content of 5-HIAA, these results would appear to cast doubt on the hypothesis that 5-HT systems play a critical role in the pathogenesis of extrapyramidal dysfunction occurring in either Parkinson's or Huntington's disease.

Attempts to stimulate serotonergic function by precursor loading have also been widely used to evaluate the functional role of serotonergic systems in man. When given to parkinsonian patients, *L*-5-hydroxytryptophan in combination with a peripheral decarboxylase inhibitor, or *L*-tryptophan together with pyridoxine exacerbates parkinsonian signs (10, 13). On the other hand, *L*-tryptophan by itself, even at relatively high dose levels, has no obvious effect on motor

function in parkinsonian patients (6). Although choreatic movements in patients with Huntington's disease are reportedly increased by *L*-5-hydroxytryptophan (15), the administration of *L*-tryptophan has no observable effect (5). The foregoing observations provide additional support for the contention that 5-HT mechanisms are not significantly involved in producing chorea in Huntington's disease patients; however, their interpretation in parkinsonian patients is far less certain. Although the findings with *L*-5-hydroxytryptophan or with *L*-tryptophan plus pyridoxine as well as those involving reductions in 5-HIAA levels in spinal fluid might suggest that alterations in serotonergic mechanisms affect human extrapyramidal function, the results with parachlorophenylalanine or with *L*-tryptophan without pyridoxine appear inconsistent with this view. Since precursors for 5-HT and dopamine compete for uptake and metabolism in the CNS, it is possible that the clinical effects of *L*-5-hydroxytryptophan or *L*-tryptophan (when given with the cofactor of one of the enzymes involved in its conversion to 5-HT) in parkinsonian patients reflect diminished dopaminergic function rather than an enhancement of 5-HT-mediated activity.

Certain of the difficulties attending the interpretation of results from clinical trials involving precursor loading might be overcome by studies using drugs which act as direct 5-HT receptor agonists. The pharmacologic activity of agents of this type should be relatively independent of the functional integrity of the presynaptic neuron and thus effective in situations where a reduction in serotonergic transmission arises as a consequence of the degeneration of 5-HT-containing nerve terminals. Fenfluramine, a widely used anorectic agent, appears to act centrally to augment 5-HT-mediated synaptic function. Preclinical observations suggest that this activity reflects either or both a direct stimulatory effect on postsynaptic 5-HT receptors or inhibition of the reuptake of 5-HT released into the synaptic cleft (16). As expected of a drug acting by either of these mechanisms (1, 2), neurologic patients receiving brief therapeutic trials of fenfluramine had marked reductions in their probenecid-induced accumulation of 5-HIAA (16). No consistent alteration in choreatic movements attended the administration of fenfluramine to patients with Huntington's disease (9).

*Behavioral Function*

In this double-blind study, fenfluramine treatment was, however, associated with a significant reduction in caloric intake and body weight (16). In addition, twice daily ratings of eight behavioral parameters revealed a significant increase in both somnolence and depression scores (9). Further statistical analysis of these results suggested that the effects on these two behavioral functions were not significantly interrelated.