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Editorial

Serotonin (5-HT) has provided a rich source of investigation for researchers engaged in understanding basic aspects of CNS function, and particularly those involved in CNS drug discovery. Of the latter, the value of this research can be demonstrated by the fact that of the top 10 CNS drugs in terms of worldwide sales in the year 2000, seven rely on serotonin receptor modulation for at least one component of their mechanism of action. These include the selective serotonin reuptake inhibitors (SSRIs: Prozac, Seroxat, Zoloft), the mixed SSRI/SNRI venlafaxine (Effexor), the atypical neuroleptics (Zyprexa, Risperidal) and the prototype triptan — sumatriptan (Imigran) (source IMS: data based on prescription sales). This point is emphasised in the clinical overview of 5-HT-based therapeutics by Jones and Blackburn.

It should be remembered that these drugs were discovered and developed at a time when our knowledge of the pharmacology and function of this transmitter system was considerably less than what it is now. Thus, as Hoyer, Hannon, and Martin describe in their review, since the early 1990s, 14 serotonin receptors have been cloned and sequenced — a number that has remained relatively unchallenged over the last few years. Armed with this extended pharmacological insight, the subsequent availability of receptor subtype knockout mice, and the discovery of various receptor subtype selective drugs as pharmacological tools — one can only hope that a better understanding of CNS serotonin function will emerge. For instance, we may begin to gain a clearer understanding into the ways serotonin regulates such higher functions as cognition and mood and consequently understand why 5-HT-based drugs sell so well as therapies for depression, anxiety, and psychosis. Such improved knowledge may hopefully lead to improved serotonin-based therapies with either better side-effect profiles, onset rates, or efficacy — or alternatively a better understanding of the actual disorders and target population treatable by such drugs.

It is with this hope that we felt the time was appropriate for an update on serotonin and the pharmacological, biochemical, and behavioural effects associated with this neurotransmitter. We requested a variety of articles addressing a diverse range of topics. These cover both applied studies aimed at discovering the potential antidepressants and antipsychotics of the future, to understanding how serotonin influences such fundamental behaviours as feeding and timing.

Regarding novel 5-HT-based therapeutics, a variety of papers describe the evaluation of 'tool' compounds to investigate the potential of various 5-HT receptors as drug targets for a variety of CNS indications. For instance, papers by DiMatteo et al., Smith et al., and Martin et al., examine the anxiolytic and antidepressant potential of selective 5-HT_{2C} receptor antagonists. Stean et al. and Pouzet et al. describe a series of studies examining the procognitive and antipsychotic potential of 5-HT_6 receptor antagonists. The studies of Stean et al. are particularly interesting in that the studies designed to investigate the therapeutic potential of this drug class are performed in tandem with pharmacodynamic assays to provide a measure of target occupancy. In a separate article, Pouzet et al. also present a detailed investigation into the antipsychotic potential of 5-HT_7 receptor antagonists, using the tool compound SB-258741. De Deurwaerdere et al., using the selective 5-HT_4 antagonists GR125487 and GR113808, explore the interaction between this subtype and behaviours related to nigrostriatal DA transmission. Lin and Parsons describe an anxiogenic-like effect of 5-HT_{1B} receptor activation and suggest that this receptor may represent a potential therapeutic target for treating anxiety. The combination of intracerebral microinjection techniques with appropriate tool compounds to explore this receptor subtype on behaviour is presented by Martinez-Clarke and Geyer. Finally, Millan and colleagues present two papers outlining binding (Millan et al.) and behavioural (Brocco et al.) assays, which may have value for the discovery of future serotonin-based therapeutics.

Serotonin has long been known to be involved in the control of feeding behaviour, and this area of research is well represented in this issue. The article by Hewitt et al. is concerned with the role of 5-HT in satiety and points to the importance of the 5-HT_{2C} receptor subtype in mediating this aspect of feeding. Other papers clearly indicate that serotonergic control of feeding is multifaceted in terms of the receptors involved, brain sites of action, and behavioural processes. Thus, Currie et al. show that hypothalamic 5-HT_{2A} receptors modify changes in food intake and metabolism induced by neuropeptide Y. Simansky and Nicklous describe a 5-HT_{1B} receptor mechanism in the parabrachial nucleus that may be a substrate for the well-documented anorectic action of fenfluramine, and Parker et al. show that 5-HT in the amygdala, interacting with hormonal status, modifies palatability induced feeding.

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The impact of serotonin on motivated behaviours extends beyond feeding, and over recent years the notion that 5-HT may be involved in drug abuse and addiction has received considerable support. Olausson et al. review the evidence for serotonergic involvement in drug taking and addiction, with particular emphasis on nicotine. Seth et al. also contribute a review of serotonin/nicotine interactions. Still other articles show that manipulation of serotonergic function alters ethanol self-administration (Tomkins et al.), amphetamine self-administration (Fletcher et al.), and the behavioural effects of cocaine (Filip and Cunningham). At least some of the influence of 5-HT on behavioural processes related to drug abuse is likely due to interactions between 5-HT and dopamine. The review by Di Matteo et al. describes the nature of such interactions with emphasis on the role of 5-HT_{2C} receptors. Further articles by Fone and Topham, and Hajos-Korcsok and Sharp, continue the theme of serotonin interactions with other neurochemical systems—thus emphasising the broad modulatory influence of this monoamine.

Another area of historical interest for serotonin research is that of timing behaviour and its potential relevance to stimulus control and impulsivity. Bradshaw, Szabadi, and coworkers contribute both a review (Ho et al.) and an original research article (Body et al.) which addresses this topic.

The recreational drug MDMA (Ecstasy), is of particular interest to serotonin researchers because of its marked, acute effect on 5-HT release, and because of the potential neurotoxic effects of MDMA on 5-HT neurons. Parrott reviews the evidence that MDMA use in humans has several deleterious physiological and psychological consequences, and the evidence that these effects of MDMA result from disturbances in 5-HT function. It is well known that MDMA is neurotoxic to 5-HT neurons in laboratory animals. However, the issue of whether such damage occurs in human users is controversial and Kish provides a critical review of the evidence on MDMA-induced neurotoxicity in human brain.

Fenfluramine, a 5-HT releasing agent, has been used successfully in the past in the management of obesity. However, this drug was withdrawn because of reports of cardiac valvulopathy. Rothman and Baumann argue that 5-HT releasing agents may have therapeutic benefits and discuss the potential for developing such medications devoid of the side effects that plagued fenfluramine.

Although SSRIs are effective antidepressants, alleviation of mood by these drugs does not necessarily imply a cause and effect relationship between 5-HT and mood. One experimental technique that can be used in humans to explore the impact of altered 5-HT function on behaviour is tryptophan depletion. Young and Leyton review the results of studies involving this technique, and demonstrate a role for serotonin in the regulation of mood, as well as aggression.

As a final note, we would like to thank the many colleagues who have helped to put together this issue, particularly those who have reviewed these articles — often at short notice. Without their support this project would have been considerably harder to complete. We would also like to extend our appreciation to the various individuals who have contributed articles. Clearly, the present issue covers a diverse range of topics, commensurate with the diverse range of contributors — from Pharma to academia, the preclinical to clinical setting. Consequently, we hope this Special issue may serve as a broad guide to serotonin research in the year 2002.

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