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EDITORIAL

Serotonin revisited

Philip J. Cowen · Irwin Lucki

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Serotonin (5-HT) pathways in the brain continue to be an important target for psychotropic drug development as well as the object of studies aimed at understanding the pathophysiology of psychiatric and neurological disorders. The discovery of multiple receptor subtypes for serotonin has led to an explosion of research to identify correspondent functions. Thus, as further selective ligands are developed, the function of the various receptor subtypes can be probed and elucidated. In this special issue of psychopharmacology, the functions of serotonin are revisited in light of new tools and discoveries.

The arrival of new pharmacological tools introduces novel targets for the many behavioural effects linked with serotonin. 5-HT_6 receptors are associated with cognition (Kendall et al. 2011), as well as antidepressant and anxiolytic effects (Carr et al. 2011), while 5-HT_4 receptors are linked to appetite suppression (Francis et al. 2011). New roles for serotonin receptor subtypes and modulators of serotonin transmission are suggested in animal models of aggressive behaviour (Takahashi et al. 2011).

Serotonin receptor subtypes may also play an important role in antipsychotic drug development targeted at improvements of cognition in schizophrenia (Meltzer et al. 2011). Of course, it is well known that 5-HT_{2A} receptor antagonist properties are a prominent part of the pharmacological profile of many clinically used antipsychotic drugs, but how far this action contributes to therapeutic effects, needs clarification; this is explored in the study of Rasmussen et al. (2011). The role of serotonin receptors in substance abuse is highlighted in two papers. Serotonin receptors are shown to be involved in behavioural sensitization to cocaine (Zayara et al. 2011); and the reinstatement of cocaine-seeking behaviour, a model for treatment relapse, involves 5-HT_{2A} receptors in the frontal cortex (Pockros et al. 2011). Finally, dopamine transmission is important in both schizophrenia and substance abuse, and the differential roles of serotonin receptor subtypes in regulating dopamine transmission are reviewed (Navailles and De Deurwaerdére 2011).

Despite undoubted progress in animal experimental studies, clinical application of serotonin pharmacology has not yet lived up to its initial promise. While selective serotonin reuptake inhibitors (SSRIs) are the most widely used drugs worldwide for the treatment of depression and anxiety, their efficacy is widely regarded as modest in terms of achieving clinical remission (Anderson et al. 2008). Whether some SSRIs are more effective than others, has been a persistently rehearsed question to which the paper of Ou and colleagues (2011) addresses itself.

Perhaps more pertinent is the observation that newer serotonin agents have not supplanted the SSRIs in the treatment of anxiety and depression. The notion that combining an SSRI action with additional agonist or antagonist activity in serotonin receptor subtypes will improve efficacy and tolerance is intriguing (Carr and Lucki 2011) but not yet established in clinical populations. Clinically, the notion that clinical depression is caused by diminished serotonin function has clearly been an oversimplification.

P. J. Cowen (✉)
University Department of Psychiatry, Warneford Hospital,
Oxford OX3 7JX, UK
e-mail: phil.cowen@psych.ox.ac.uk

I. Lucki
Department of Psychiatry, University of Pennsylvania,
125 South 31st Street, Room 2204,
Philadelphia, PA 19104, USA

The best evidence for such, as effect comes from studies of tryptophan depletion (Ruhe et al. 2007), a technique, which was pioneered in humans through a seminal paper published 25 years ago in *Psychopharmacology* by Simon Young (Young et al. 1985). Tryptophan depletion continues to be an important technique for examining the role of serotonin pathways in human neuropsychology and in various clinical disorders, as shown by several papers published in this special issue.

The tryptophan depletion data in depression provide sufficient evidence for involvement of serotonin neurones to merit further investigation with new brain imaging techniques made possible by the development of labelled subtype selective serotonin ligands. Two examples of this approach are published in the current issue, and clear findings seem to emerge of changes in the serotonin transporter and 5-HT_{1B} receptor (Selveraj et al. 2011; Murrough et al. 2011). However, it must be acknowledged that even state-of-the-art imaging methodology with highly selective ligands has not revealed a particularly consistent pattern of serotonin receptor abnormalities in major depression (Drevets et al. 2007; Parsey et al. 2010). The reason for this unsatisfactory state of affairs probably rests with issues such as clinical heterogeneity and the effects of previous drug treatment. Methodological factors, such as the precise choice of reference tissue, might also be a factor. Whatever is the cause, it has made it difficult to place the role of serotonin in the pathophysiology of depression on a sound experimental footing.

While we know much about the influence of serotonin on certain well-characterised behaviours, for example feeding and anxiety, a formulation of the overall neuropsychological function of serotonin pathways is still elusive, sometimes bringing to mind the memorable comment of Barry Jacobs that serotonin is involved in virtually everything, but responsible for nothing (Jacobs and Fornal 1995). More recently, a number of interesting ideas have been proposed, focusing on the effects of serotonin pathways to modify punished responding perhaps by acting in opposition to dopamine. Seen in this way, serotonin may modulate the affective impact of punishment-related signals and also promote response inhibition (Cools et al. 2007; Boureau and Dayan 2010). The paper by Fitzgerald (2011) provides an interesting development of this approach by examining the role of serotonin in prefrontal cortex in relation to noradrenaline.

Serotonin continues to be a vibrant research area with much left to discover about the physiological role and clinical importance of this fascinating neurotransmitter. A long road probably remains, but even psychopharmacologists can be encouraged by the reported comment of Albert Einstein: 'It's not that I'm so smart, it's just that I stay with problems longer.'

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