Serotonin in Anxiety and Depression

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Over 20 years ago JF William Deakin (University of Manchester) and Frederico G Graeff (University of São Paulo) published in this journal their theory on the behavioural functions of the dorsal and median raphe serotonin subsystems in modulating basic brain mechanisms of defence. They perceived these functions as unified in serving to terminate or minimise contact with aversive stimuli. Deakin and Graeff (1991), reproduced here, made explicit predictions about the brain systems engaged by different behavioural anxiety paradigms, such as the elevated plus maze and conditioned fear, and how dysfunction results in psychiatric disorders such as panic, depression and generalised anxiety.

Deakin (this issue) describes how the theory developed from Fred Graeff’s early work in the late 1970s via a series of visits and collaborative experiments between Brazil and Manchester up to its publication. He describes how subsequent human psychopharmacological and imaging studies are broadly compatible with the theory.

Paul and Lowry (this issue) show how animal behavioural responses to different forms of aversion can be mapped onto much finer subdivisions of the raphe than envisaged by Deakin and Graeff. Concerning the dorsal raphe nucleus (DRN), the authors suggest that, while the dorsal/caudal parts project to forebrain limbic areas involved in conflict anxiety-related responses, the lateral portions send inhibitory projections to structures that control fight-or-flight responses. In keeping with this idea, de Bortoli et al. (this issue) report that these behavioural responses, when induced by electrical stimulation of the dorsal medial hypothalamus, are phasically inhibited by activation of 5-HT1a and/or 5-HT2a receptors located within this area, as has been shown in the dorsal periaqueductal grey (dPAG). These authors also suggest that the anti-panic effects of antidepressant drugs may be due to facilitation of 5-HT neurotransmission systems in hypothalamic components of the brain aversion system. Rezende et al. (this issue) present the human equivalent, that anxiety evoked in the Simulated Public Speaking Test was increased after acute administration of sumatriptan, a 5-HT1D/1B agonist which decreases serotonin release.

Paul and Lowry (this issue) present new data on the Deakin and Graeff idea that median raphe projections mediate antidepressant-like tolerance and adaptation to chronic aversive events and that the dorsal continuation into the interfascicular part of the dorsal raphe nucleus is part of this system. Andrade et al. (this issue) point out that the serotonin projections arising in the median raphe nucleus that innervate the dorsal hippocampus are involved in the regulation of anxiety. Using an animal model of depression, the forced swim test, Almeida et al. (this issue) suggest that adaptation to the inescapable and stressful situation represented by the forced swim may be mediated, at least in part, by non-5-HT1a receptors, since the 5-HT1a antagonist WAY100635 did not block the effects of 8-OH-DPAT, a 5-HT1a agonist.

Serotonin interactions with other systems are discussed in several contributions. Roncon et al. (this issue) suggest that proximal defence is regulated by an interaction between 5-HT1a and µ-opioid receptors in post-synaptic neurons in the dPAG. Twardowschy et al. (this issue) show that the anti-escape (“panicolytic”) effects of cannabidiol are mediated through 5-HT1a receptors in the presence of threatening stimuli, such as a snake in the prey–predator interaction paradigm.

Interactions between the serotoninergic and gamma-aminobutyric acid (GABA)ergic systems on the expression of contextual fear (fear potentiated startle) are discussed by Almada et al. (this issue). Activation of 5-HT1a receptors within the dorsal hippocampus 24 hours after training did not affect expression of contextual fear, while blocking of GABAergic receptors did. Restell et al. (this issue) show that PAG nitric oxide and glutamate signalling modulate the expression of contextual fear.

Juruena et al. (this issue) describe clinical experiments on the role of high cortisol levels in treatment-resistant depression. Down-regulation of mineralocorticoid receptors may be involved, with possible roles of aldosterone and sex hormones. Lovick discusses the positive influence of selective serotonin receptor inhibitors on phasic menstrual cycle-linked symptoms such as premenstrual syndrome and catamenial epilepsy in women during late luteal phase.

The papers in this issue reflect what was a very stimulating conference. They demonstrate the continuing interest in elaborating the role of serotonin subsystems in adaptive responses to aversion and in psychiatric disorders in the 20 years following Deakin and Graeff.