

Editorial

Serotonergic Systems in Anxiety

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Most work in the neurochemistry of anxiety has focused on the monoamines 5-HT and NA, the GABA-benzodiazepine (BDZ) receptor complex and a number of unrelated challenge compounds that are known to provoke anxiety and/or panic (e.g. cholecystokinin, sodium lactate, caffeine). Interest in the GABAergic; 5-HTergic and NAergic systems originates from the clinical efficacy of compounds affecting these systems in the treatment of anxiety states and the study of their agonists and antagonists in the provocation and prevention of anxiety.

5-HT has been implicated in the neurochemistry of anxiety for a long time, but interest in it has increased dramatically in the past 10 years for a number of reasons: the introduction in clinical practice of the non-benzodiazepine anxiolytic buspirone, and the widespread use and success of ADs, in particular the SSRIs for treating anxiety disorders). The development of specific ligands for 5-HT receptors allows the visualization and the study of the multiplicity of 5-HT receptors and their functional role in disease. Further, the use of the tryptophan depletion technique in humans and molecular manipulation, and microdialysis studies in animals allow for a more rigorous assessment of the integrity of the 5-HT system in the CNS.

The original hypothesis of the role of serotonin in the pathogenesis of anxiety stems from observations of 5-HT antagonists in operant models and an association between a reduction in 5-HT turnover and the anxiolytic effects of benzodiazepines, concluding that a reduction of 5-HT neurotransmission results in an anxiolytic-like effect, whereas increased activity produces an anxiogenic-like effect. Inhibition of postsynaptic 5-HT₁, 5-HT₂ and 5-HT₃ receptor subtypes has since provided extensive support for this hypothesis. However the behavioral effects of drugs altering the activity of the central 5-HT system are often more variable and challenge paradigms that increase central 5-HT transmission produced mixed results. The 5-HT agonist meta-Chlorophenylpiperazine (mCPP) is anxiogenic in patients with panic disorder, obsessive compulsive disorder, generalized anxiety and in normal controls at high enough doses. Fenfluramine, a drug that releases 5-HT is also anxiogenic in panic disorder. On the other hand, SSRIs are believed to exert their action by increasing the availability of the transmitter in the synaptic cleft. L-tryptophan and 5-hydroxytryptophan, the precursors of 5-HT, are known to cause sedation and anxiolysis, or at worst, to have no effect on anxiety. Thus not all findings are accounted for by the classic hypothesis and it is not clear yet whether anxiety results from excessive or deficient central

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serotonin function.

A different hypothesis of the role of serotonin in anxiety emphasizes the link between low 5-HT and its association with hypersensitivity to environmental cues and increased responsiveness to threat. Soubrie (1986) has argued that a decrease in serotonergic transmission leads to an inability to adopt passive or waiting attitudes or to accept situations that necessitate or create strong inhibitory tendencies.

Collating this information into a coherent theory represents a number of problems and it is now accepted that the hypotheses that anxiety is secondary to excessive or diminished 5-HT activity is being challenged by more sophisticated models. These models place less emphasis on global levels, but see different serotonergic neural circuitry and receptors mediating different aspects of anxiety. Thus 5-HT released from nerve terminals from the dorsal raphe nucleus (DRN) is supposed to increase learned anxiety in the amygdala, whereas 5-HT released from DRN terminals innervating the periaqueductal gray (PAG) would inhibit unconditioned fear. The amygdala would be mainly responsible for conditioned fear (avoidance). Dysfunctional activation of these mechanisms would result in the anxiety state in human beings, known as GAD. In contrast the PAG would organize the response to unconditioned aversive stimuli. Clinically its dysfunction would result in panic disorder. The response of these two systems to changes in availability of 5-HT are quite different. Thus, increases in 5-HT at the PAG are thought to inhibit panic whereas those at the amygdala are thought to be anxiogenic.

Some support for the Deakin and Graeff model is lent by experiments showing that 5-HT promoting agents (fenfluramine and mCPP) increase skin conductance in a paradigm of an aversive conditioned stimulus (loud tone) in healthy volunteers. On the other hand, a 5-HT blocking agent (ritanserin) had exactly the opposite effect. The microinjection of 5-HT antagonists into the basolateral amygdala was shown to release water licking suppressed by electric shock punishment. Microinjection of 8-OH-DPAT into the same area of the amygdala has been reported to further decrease punished lever pressing in a modified Geller-Seifter procedure. Evidence for the involvement of the periaqueductal gray in panic comes from studies in both animals

and humans. Electrical stimulation of the PAG in laboratory animals induces defensive reactions, such as vigorous flight or defensive aggression and induces panic-like symptoms in neurosurgical patients. Different ways of increasing 5-HT activity in the PAG had an anti-aversive effect (electrical stimulation of the DRN, whereas 5-HT depletion resulted in facilitation of escape from PAG electrical stimulation (para-chloro-phenylalanine; (PCPA). It is not clear yet whether these different anatomical systems are associated with different 5-HT receptor subtypes that would make pharmacological manipulation possible. Most of the work in this field has been carried out in animal models so far and some controversy remains, depending on the mode of administration, as 5-HT₂ and 5-HT₁ receptors were found to both facilitate and inhibit aversion induced by electrical stimulation of the PAG.

Finally evidence for the molecular/genetic processes involved in the regulation of the central 5-HT system and their significance for anxiety have begun to emerge. A polymorphism of the 5-HT transporter (SERT) gene has been associated with anxiety personality traits. Further advances in neuroimaging hold the promise of delineating the pathophysiology of the fear pathway in patients with anxiety disorders in vivo, shedding light on the proposed homology with preclinical models. Much may also be gained at the basic science level in terms of clarifying the role of the various 5-HT receptor subtypes and their modulation by both acute and chronic administration of serotonergic ligands.

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