

## S54. New vistas in challenge paradigms in anxiety disorders

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### EXPERIMENTAL MODELS OF ANXIETY

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Deakin and Graeff (D&G; [1]) proposed that 5HT has different roles in different forms of anxiety. The dorsal raphe nucleus innervates 5HT<sub>2</sub> and 5HT<sub>1D</sub> receptors in dopaminergic structures — basal ganglia, amygdala and frontal cortex. D&G suggest this system is activated by distal or conditioned aversive stimuli to facilitate anticipatory anxiety associated with freezing and avoidance behaviour. D&G predict the DRN system is overactive in generalised anxiety disorder. In contrast, proximal aversive stimuli such as pain and asphyxia elicit the fight-flight reflex mediated by the amygdala-hypothalamic-periaqueductal grey Brain Aversion System (BAS). Panic attacks may be due to spontaneous activation of the BAS. D&G propose the BAS is held in check by DRN 5HT projections to mediate behavioural inhibition during anticipatory anxiety. This theory has survived a number of tests in normal volunteers which have examined the effects of drug-induced manipulations of 5HT function in three forms of experimental anxiety (n always > 15 per group).

Agonists at 5HT<sub>2</sub> receptors (fenfluramine and mCPP) facilitated aversive conditioning (AC) of skin conductance responses to initially neutral tones after the tone was paired with an aversive (100 Db, 1 sec) white noise. The antagonist ritanserin blocked conditioning. The results are compatible with the proposed role of DRN-5HT<sub>2</sub> in anticipatory anxiety. The same drugs had opposite effects when tested on self-rated anxiety evoked by an unexpected demand to prepare a speech (simulated public speaking; SPS). Most strikingly, fenfluramine caused a dose-dependent anxiolytic effect [2] as predicted by the proposed restraining influence of 5HT on the BAS.

5HT appears also to restrain anxiety evoked by breathing 5% CO<sub>2</sub>. Patients were tested on two occasions. Self-rated anxiety (Acute Panic Inventory) increased after CO<sub>2</sub> in Patients with DSM-III panic disorder and in controls. The anxiogenic effect was significantly enhanced after depletion of circulating tryptophan by 75% induced by the anabolic response to a drink of amino-acids.

[1] Deakin JFW, Graeff FG (1991) *J. Psychopharmacol.* 5, 305–315.

[2] Hetem LAB et al (1993) *Braz. J. Med. Biol. Res.* 26, 971–973.

### SEROTONERGIC AND CHOLECYSTOKININERGIC CHALLENGES IN PANIC DISORDER

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Clinical studies have shown that an i.v. bolus injection of the tetrapeptide CCK-4, a CCK-B receptor agonist, is able to induce panic attacks in patients with PD and healthy controls.

To further substantiate the role of CCK-B receptors in PD we conducted a study with the selective CCK-B receptor antagonist L-365,260. In this collaborative study we found a panic rate for CCK-4 of 86% after pretreatment with placebo, 33% for 10 mg L-365,260 and 0% for 50 mg of L-365,260, indicating that the CCK-B antagonist L-365,260 can effectively block panic attacks induced by

CCK-4, which raises the possibility that CCK-B antagonists could be effective anxiolytic agents. We also investigated the ability of the CCK-B antagonist L-365,260 in blocking lactate induced panic attacks. A double-blind placebo-controlled parallel group design was used. Twenty four patients with PD were given either a single oral dose of 50 mg L-365,260 (N = 12) or placebo (N = 12). In patients who received placebo as a pretreatment 6/12 patients panicked versus 3/9 in the L-365,260 group. L-365,260 was different from placebo on all anxiety measures, in that less anxiety was reported, although only with respect to the item 'apprehension' on the Panic Symptom Scale, this difference was statistically significant. This study suggests that the CCK-B antagonist L-365,260 was able to prevent the anxiogenic effects of i.v. administration of lactate, and substantiates its possible role as an anxiolytic.

In view of the interaction between 5-HT and CCK neuronal systems, we studied the effects of the selective 5-HT reuptake inhibitor fluvoxamine on CCK-4 induced panic. A double blind placebo controlled study was conducted in which 24 patients suffering from PD were challenged with an i.v. bolus injection of 50 µg CCK-4 before and after treatment with 8 weeks fluvoxamine (150 mg). After treatment, the number of panic attacks induced by CCK-4 in those patients who responded to treatment with fluvoxamine, was significantly lower as compared to non-responders. Future studies with more specific 5-HT receptor ligands will shed more light on the 5-HT receptor subtypes which may, in addition to CCK-B receptors, play a role in CCK-4 mediated anxiety.

### IMAGING STUDIES IN ANXIETY DISORDERS

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The new imaging technologies of PET, SPECT and fMRI offer for the first time the possibility of defining the brain circuits and neurotransmitter systems involved in the production and control of the various forms of anxiety. Most work so far has used (regional cerebral blood flow; rCBF) as a measure activation during anxiety. The first PET studies of panic disorder and experimentally-induced anxiety found increased activation in the region of the temporal lobes. These results were questioned because of the contribution of muscle activity included in the results because of the poor resolution of the scanner. However, later studies with both HMPAO SPECT and <sup>15</sup>O-water PET have found that exposure of either simple phobics or patients with OCD to feared stimuli alter rCBF in the temporo-occipital and orbito-frontal lobes. Our own studies have used an anxiety-conditioning paradigm that allows repeated <sup>15</sup>O-water scanning in anxious and control states. The paradigm generated anxiety by conditioning to mild electric shocks and produced clear increases in subjective and autonomic measures of anxiety. Several brain regions including orbito-frontal cortex, insula (bilaterally), anterior cingulate, periaqueductal grey matter and several regions of the cerebellum (cortex (bilaterally), central nuclei and vermis) are activated by this paradigm. Thus our new conditioning paradigm has delineated brain circuits previously thought to be involved in anxiety and mood (e.g. PAG, insula, cingulate) plus some probably involved in learning (cerebellum). It offers the opportunity to study the circuits of anxiety acquisition in pathological anxiety states and to explore the effects of treatments on these. Future prospects involve the use of "hot ligand" PET and SPECT tracers (eg those labelling benzodiazepine receptors) to understand the neurotransmitter basis for anxiety-induced activations of these circuits.

[1] Malizia, AL & Nutt, DJ. (1995) Functional neuroimaging studies in human anxiety disorders. *Acta Neuropsychiatrica* 7(3): s42–s46.