New vistas in challenge paradigms in anxiety disorders

Chairmen: J.A. den Boer, D Nutt

EXPERIMENTAL MODELS OF ANXIETY


Deakin and Graeff (D&G; [1]) proposed that 5HT has different roles in different forms of anxiety. The dorsal raphe nucleus innervates 5HT2 and 5HT1D 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 5HT2 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-5HT2 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% CO2. Patients were tested on two occasions. Self-rated anxiety (Acute Panic Inventory) increased after CO2 in Patients with DSMIII 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.


SEROTONERGIC AND CHOLECYSKININERGIC CHALLENGES IN PANIC DISORDER

J.A. Den Boer, H.J.G.M. Van Megen, H.G.M. Westenberg, Department of Psychiatry, Academic Hospital, PO-Box 85300, 3508 GA Utrecht, The Netherlands

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

D.J. Nutt, A.L. Malizia. University of Bristol, Psychopharmacology Unit, School of Medical Sciences, University Walk, Bristol BS8 1TD

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 [123I]iodoamphetamine (labeled benzodiazepine receptors) to understand the neurotransmitter basis for anxiety-induced activations of these circuits. This paradigm has delineated brain circuits previously thought to be involved in anxiety and mood (e.g. PAG, insula, cingulate) plus some probably related to exploration of the effects of treatments on these. Future prospects involve the use of "hot ligand" PET and SPECT tracers (e.g those labelling benzodiazepine receptors) to understand the neurotransmitter basis for anxiety-induced activations of these circuits.


https://doi.org/10.1016/0924-9338(96)88606-8 Published online by Cambridge University Press