MOOD DISORDERS

Averting panic attacks

Benzodiazepines, which exert rapid anxiolytic effects by modulating GABA (γ-aminobutyric acid)-mediated neurotransmission, are widely used to treat anxiety disorders, but are limited by side effects, including sedation and the development of tolerance and withdrawal symptoms after prolonged use. Reporting in *Science,* Rupprecht and colleagues now show that ligands of the translocator protein (18 kD) have robust and rapid anxiolytic activity in humans without the undesirable effects of benzodiazepines.

The translocator protein (18 kD) is located on the outer mitochondrial membrane, where it facilitates cholesterol transport into the organelle and neurosteroid biosynthesis. Such endogenous metabolites have been shown to allosterically modulate GABA receptors, and their concentration is markedly reduced during panic attacks, but their therapeutic potential has remained largely unexplored.

Previous studies found that a compound known as XBD173 displayed high affinity and selectivity for the translocator protein (18 kD) and exerted anxiolytic effects in rodents. In this paper, the authors examined the effects of this compound in mouse brain and showed that XBD173 enhanced GABA-mediated neurotransmission. Further preclinical studies showed that the compound counteracted experimentally induced panic-like anxiety (with lactate or CCK4 (also known as PTK7)) in rats without inducing sedation or tolerance development.

This led the authors to carry out a small trial in healthy human volunteers subjected to a CCK4 challenge. Acute Panic Inventory scores after a first CCK4 challenge were compared with those obtained after a second challenge presented following 7 days of treatment with placebo, the benzodiazepine alprazolam or XBD173. Not only did the authors find similar anxiolytic effects in the XBD173- and the alprazolam-treated groups, but also the number of side effects reported with XBD173 was similar to the placebo-treated group. By contrast, a high incidence of dizziness and drowsiness was reported by the alprazolam-treated subjects. Moreover, there were no withdrawal symptoms after discontinuation of XBD173 — in contrast to alprazolam, which provoked withdrawal symptoms after only 7 days of treatment.

Given that long-term use of benzodiazepines is limited by their side effects, and that selective serotonin reuptake inhibitors, the main current alternative treatment for anxiety disorders, take several weeks to have an effect, drugs that have rapid anxiolytic effects but lack the side effects of benzodiazepines are desirable. Overall, this study suggests that targeting the synthesis of neurosteroids with agents such as XBD173 could be another promising strategy in the quest to develop such drugs.

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ORIGINAL RESEARCH PAPER Rupprecht, R. *et al.* Translocator protein (18kD) as a target for anxiolytics without benzodiazepine-like side effects. *Science* 18 Jun 2009 (doi:10.1126/science.1175055)
FURTHER READING Sanacora, G. *et al.* Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nature Rev. Drug Discov.* **7**, 426–437 (2009)