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VORTIOXETINE, AN INVESTIGATIONAL ANTIDEPRESSANT: IMPLICATIONS OF ITS MULTIMODAL MECHANISM OF ACTION IN PRECLINICAL MODELS OF DEPRESSION AND COGNITIVE FUNCTION

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Background: Vortioxetine is a 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter (SERT).
Objectives: To study the in vitro properties of vortioxetine at rat and human targets and relate them to rat brain target occupancies and effects in rat models assessing antidepressant activity and cognitive function.
Methods: The in vitro properties were assessed using radioligand binding and cell-based functional assays, brain target occupancies were studied using ex vivo autoradiography, antidepressant activity was studied in conventional behavioural models and in a progesterone withdrawal model, and effects on cognitive function were assessed by quantitative EEG [qEEG] and after 5-HT depletion in recognition and spatial memory tasks.
Results: Vortioxetine was more potent at human than rat 5-HT_{1A} and 5-HT_7 receptors and the SERT, whereas the opposite was found for 5-HT_{1D} and 5-HT_3 receptors. The rat in vitro and ex vivo potency rank orders were aligned. Vortioxetine showed antidepressant activity in conventional models and the fluoxetine-insensitive progesterone withdrawal model. qEEG analyses demonstrated increases across power bands with vortioxetine, but not duloxetine or escitalopram. Vortioxetine restored memory deficits induced by low 5-HT, whereas duloxetine and escitalopram had no effect.
Conclusions:
1. Species comparisons of target activities and inclusion of target occupancy measures in animal studies supports the translation from preclinical to clinical settings.
2. Vortioxetine exerts antidepressant and memory-enhancing effects in rats via mechanisms beyond that of SERT inhibition.

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