World Academy of Science, Engineering and Technology
International Journal of Cognitive and Language Sciences
Vol:16, No:10, 2022

The 5-HT1A Receptor Biased Agonists, NLX-101 and NLX-204, Elicit Rapid-Acting Antidepressant Activity in Rat Similar to Ketamine and via GABAergic Mechanisms

Authors : A. Newman-Tancredi, R. Depoortère, P. Gruca, E. Litwa, M. Lason, M. Papp

Abstract : The N-methyl-D-aspartic acid (NMDA) receptor antagonist, ketamine, can elicit rapid-acting antidepressant (RAAD) effects in treatment-resistant patients, but it requires parenteral co-administration with a classical antidepressant under medical supervision. In addition, ketamine can also produce serious side effects that limit its long-term use, and there is much interest in identifying RAADs based on ketamine's mechanism of action but with safer profiles. Ketamine elicits GABAergic interneuron inhibition, glutamatergic neuron stimulation, and, notably, activation of serotonin 5-HT1A receptors in the prefrontal cortex (PFC). Direct activation of the latter receptor subpopulation with selective 'biased agonists' may therefore be a promising strategy to identify novel RAADs and, consistent with this hypothesis, the prototypical cortical biased agonist, NLX-101, exhibited robust RAAD-like activity in the chronic mild stress model of depression (CMS). The present study compared the effects of a novel, selective 5-HT1A receptor-biased agonist, NLX-204, with those of ketamine and NLX-101. Materials and methods: CMS procedure was conducted on Wistar rats; drugs were administered either intraperitoneally (i.p.) or by bilateral intracortical microinjection. Ketamine: 10 mg/kg i.p. or 10 µg/side in PFC; NLX-204 and NLX-101: 0.08 and 0.16 mg/kg i.p. or 16 µg/side in PFC. In addition, interaction studies were carried out with systemic NLX-204 or NLX-101 (each at 0.16 mg/kg i.p.) in combination with intracortical WAY-100635 (selective 5-HT1A receptor antagonist; 2 µg/side) or muscimol (GABA-A receptor agonist, 12.5 ng/side). Anhedonia was assessed by CMS-induced decrease in sucrose solution consumption; anxiety-like behavior was assessed using the Elevated Plus Maze (EPM), and cognitive impairment was assessed by the Novel Object Recognition (NOR) test. Results: A single administration of NLX-204 was sufficient to reverse the CMS-induced deficit in sucrose consumption, similarly to ketamine and NLX-101. NLX-204 also reduced CMS-induced anxiety in the EPM and abolished CMS-induced NOR deficits. These effects were maintained (EPM and NOR) or enhanced (sucrose consumption) over a subsequent 2-week period of treatment. The anti-anhedonic response of the drugs was also maintained for several weeks Following treatment discontinuation, suggesting that they had sustained effects on neuronal networks. A single PFC administration of NLX-204 reversed deficient sucrose consumption, similarly to ketamine and NLX-101. Moreover, the anti-anhedonic activities of systemic NLX-204 and NLX 101 were abolished by coadministration with intracortical WAY-100635 or muscimol. Conclusions: (i) The antidepressant-like activity of NLX-204 in the rat CMS model was as rapid as that of ketamine or NLX-101, supporting targeting cortical 5-HT1A receptors with selective, biased agonists to achieve RAAD effects. (ii)The anti-anhedonic activity of systemic NLX-204 was mimicked by local administration of the compound in the PFC, confirming the involvement of cortical circuits in its RAAD-like effects. (iii) Notably, the effects of systemic NLX-204 and NLX-101 were abolished by PFC administration of muscimol, indicating that they act by (indirectly) eliciting a reduction in cortical GABAergic neurotransmission. This is consistent with ketamine's mechanism of action and suggests that there are converging NMDA and 5-HT1A receptor signaling cascades in PFC underlying the RAAD-like activities of ketamine and NLX-204. Acknowledgements: The study was financially supported by NCN grant no. 2019/35/B/NZ7/00787.
Keywords : depression, ketamine, serotonin, 5-HT1A receptor, chronic mild stress
Conference Title : ICBNP 2022 : International Conference on Behavioral Neuroscience and Psychopharmacology
Conference Location : Dubrovnik, Croatia
Conference Dates : October 06-07, 2022