Buspirone rescues MK-801-induced disruption of prepulse inhibition and temporal order recognition in mice: A repositioning approach

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Drug repositioning refers to the process of finding new uses for already approved and commercialized medications. Drug repositioning is thought to offer great advantages over the long-lasting, risky and expensive de novo drug discovery strategy, because the pharmacological and toxicological profiles of approved agents are well-characterized (Ashburn and Thor, 2004). It has been suggested that repositioned drugs may represent effective alternative compounds for the treatment of neuropsychiatric disorders for which the classical drug discovery process is hampered by the poor knowledge of the pathophysiological mechanisms (Lee and Kim, 2016). Schizophrenia is a devastating neuropsychiatric disease with poorly understood mechanisms and no effective drug treatments. Particularly, whilst the current antipsychotic medications are often effective on the positive symptoms, they are not capable of improving the negative symptoms and the cognitive deficits (Miyamoto et al., 2012). Buspirone (Buspar®) is an approved anxiolytic drug commercially available in USA, as well as in several European countries and Australia. Growing evidence suggest that buspirone, endowed with dopamine D3R/D4R antagonism and 5HT1A partial agonism, may be effective for the treatment of substance use disorders (Leggio et al., 2014, Czoty and Nader, 2015). To our knowledge, the possible antipsychotic properties of buspirone have not been extensively investigated despite its intriguing pharmacological profile, which includes dopamine receptor-mediated effects. Thus, in this work we investigated whether buspirone could rescues the prepulse inhibition (PPI) and temporal order recognition (TOR) deficits induced by a single administration of the N-methyl-D-aspartate (NMDA) receptor antagonist MK-801 in C57BL6/J mice. In this regard, animals were injected intraperitoneally (I.P.) with buspirone (3 mg/kg) and MK-801 (0.1 mg/kg), 45 min and 20 min, respectively, before the PPI test and the sample phase two (encoding phase) of the TOR test. Buspirone significantly attenuated the PPI disruption induced by MK-801 as demonstrated by the higher percentage of PPI displayed by buspirone-pretreated mice compared to MK-801-treated mice ($p < 0.001$ at 80 db of prepulse intensity, "mean ± s.e.m." 64.6% ± 4.3 vs 32.4% ± 11; N= 9-13 per group). Moreover, buspirone significantly reversed the MK-801-induced TOR deficits. Indeed, buspirone-pretreated mice spent more time exploring the less recently experienced object in comparison to MK-801-treated mice ($p<0.01$, discrimination ratio, "mean ± s.e.m." 0.17 ± 0.11 vs -0.258 ± 0.075; n= 8-10 per group). These data suggest that buspirone might be a potential therapeutic drug for treating the cognitive impairment similar to that occurring in schizophrenia; this finding seems particularly relevant, considering that cognitive dysfunction still represents an unmet need in schizophrenia. Further studied are needed to investigate the efficacy of buspirone in other schizophrenia-related dimensions, and clarify this novel mechanism of action as well as its potential therapeutic use.

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