Rapid-acting antidepressants in motivation: the effects of low-dose ketamine and the psychedelic 2,5-dimethoxy-4-iodoamphetamine (DOI) in the rat progressive ratio task.

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The global burden of MDD is increasing and problems surrounding the side-effect profile, treatment resistance and the inefficacy of antidepressants is well established. The shift away from 'gold standard' antidepressant treatments towards novel antidepressant therapies as a solution has been growing in academia, clinically and in the pharmaceutical industry. So far, the only treatment which has come to the market is esketamine and only as an adjunct therapy to other antidepressant drugs. More recently there has been a focus on psychedelic compounds; efficacy has been demonstrated in depression [1] and psychedelics have been proposed as treatments for addiction [2]. Recently a study was published on the efficacy of low-dose ketamine and psilocybin at improving motivation in low performing rats on a progressive ratio task [3], highlighting the potential efficaciousness of 'micro-dosing' on amotivation and anhedonia. The current study aims to compare low doses of the NMDA receptor antagonist ketamine as well as a low and a psychoactive dose of the psychedelic drug and the 5-HT2 agonist DOI in the progressive ratio task in rats.

Methods:

Male Sprague-Dawley rats (n=30) were trained in an operant progressive ratio task. This task is designed to measure effort-based motivation. The number of responses required to obtain a sucrose pellet is increased for successive reinforcers. The three main measures in the task: Number of lever presses, breakpoint (trial that the animal reaches) and the session time in minutes. A rat reached the break point if it failed to receive a reward for 20 minutes. The treatment groups were, ketamine (0.1, 0.5, 1mg/kg) and DOI (0.2, 1mg/kg). Drugs were administered subcutaneously (s.c.) 30 minutes before testing in a crossover design with 72 hours in between administrations to allow for drug washout, with every animal receiving each treatment once with a final n=30 per group.

Results:

The 0.1mg/kg and 0.5mg doses of ketamine significantly increased the number of lever presses ($P<0.001$ and $P<0.01$, respectively) and the breakpoint ($P<0.0001$) 30 mins after administration. Significant increases were also observed at 24 hours for lever presses ($P<0.01$, for 0.1mg/kg and 0.5mg/kg) and breakpoint ($P<0.01$, $P<0.001$, $P<0.05$, for 0.1mg/kg, 0.5mg/kg and 1mg/kg respectively). The high dose of DOI (1mg/kg) significantly decreased the number of presses ($P<0.0001$) and the breakpoint ($P<0.0001$) 30 mins after administration. DOI (1mg/kg) also significantly reduced the session time ($P<0.05$), all results were compared to baseline. Performance returned to baseline 24 hours after DOI (1mg/kg) administration. All statistical analyses were one-way repeated measures ANOVAs with Fisher's LSD post-hoc.

Conclusions:

The current studies demonstrate that an acute low dose of ketamine significantly increases motivation measured by performance in a progressive ratio task, while a psychoactive dose of the psychedelic DOI leads to an acute deficit in performance. These data suggest opposing effects of ketamine and DOI on the putative neuropsychiatric disease endophenotypes of amotivation and anhedonia. Amotivation acutely induced by DOI indicates the potential of psychedelic drugs in treating reward processing disorders, including addiction. Future studies will investigate the effects of sub-chronic dosing and long-term effects after acute dosing.

References

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