# Increased cannabinoid intravenous self-administration in the olfactory bulbectomy rat model of depression

V. Giugliano[1], P. Amchova[2], M.T. Zanda[1], S. Antinori[1], J. Kucerova[2], A. Sulkova[2], P. Fadda[1,3],W. Fratta[1,2],L. Fattore[2,3]

[1]Dept. Biomedical Sciences, University of Cagliari, Italy; [2]CEITEC-Central European Institute of Technology, Dept. Pharmacology, Masaryk University, Brno, Czech Republic; [3]Centre of Excellence 'Neurobiology of Dependence', University of Cagliari, Italy; [4]CNR Neuroscience Institute-Cagliari, National Research Council-Italy

Affective disorders and substance abuse frequently coexist as demonstrated by the high prevalence of drugs use in patients with history of major depression and other psychiatric disorders. The wide-ranging features that characterize depression are quite troublesome to reproduce in laboratory animals. However, numerous attempts have been made to develop rodent models of depression, most of which aimed at mimicking aspects of depression that are expressed as physiological and behavioural responses. The bilateral surgical removal of the olfactory bulbs results in a constellation of behavioural, neurochemical and neuroendocrine changes that are selectively reversed by chronic, but not acute, antidepressant treatments, thus validating the bulbectomized rat (OBX) as a valid animal model of depression. Clinical studies consistently showed a clear association between depression and substance abuse, a comorbidity often explained in terms of self-medication (i.e. depressed subjects take rewarding drugs to alleviate symptoms like anhedonia) or enhanced vulnerability (i.e. the neurobiological disruptions associated with depression enhance the propensity of the subject to use drugs). According to this, OBX rats have been shown to self-administer more amphetamine (Holmes et al. 2002) and methamphetamine (Kucerova et al. 2011) than sham (control) animals, confirming higher intake of psychostimulants in depressive conditions. Cannabis is one of the most commonly used drugs worldwide and its use often coexists with mental health disorders. This study was therefore undertaken to verify whether OBX rats also display higher voluntary intake of cannabinoids. To this aim, male Lister Hooded rats were either olfactory-bulbectomized (OBX) or sham-operated, and intravenous (IV) catheters were implanted 14 days after. After 1-week of recovery from IV surgery, animals started self-administration training and allowed to self-administer the cannabinoid CB1 receptor agonist WIN55,212-2 (WIN, 12.5 µg/kg/infusion) by lever-pressing and under a continuous (FR-1) schedule of reinforcement, as previously described (Fattore et al. 2001). Data showed that both OBX and sham rats develop stable cannabinoid intake. Yet, rates of responding for WIN was constantly higher in OBX than in sham rats starting soon after the first week of training. Specifically, during the last week of training (maintenance phase), the mean number of active responses was approximately 2 times higher in OBX rats (38.76±0.13) compared to control sham-operated rats (18.82±0.33). Importantly, there were no significant differences in the number of inactive responses between the two groups during the 30 days of WIN self-administration training. Moreover, while no significant differences were found between OBX and sham animals in the percentage of acquisition, OBX rats took significantly longer than sham animals to extinguish the responding for the cannabinoid after saline substitution. Although OBX rats displayed hypermobility when tested in motility cages, enhanced WIN intake by OBX rats was not associated with motor disturbances, since both locomotion within the operant boxes and the pattern of responding during operant responses were not significantly different between OBX and sham rats throughout all phases of the study (acquisition, maintenance, extinction).

Taken together, our results suggest that bulbectomized rats display alterations in cannabinoid-induced brain reward function, and strengthen the utility of the OBX model for studying the neurobiological basis of depression and drug abuse comorbidity.

Fattore et al. (2001). Psychopharmacology 156(4):410-6.
Kucerova et al. (2011). Int J Neuropsychopharmacol 15(10):1503-11
Holmes et al. (2002). Synapse 46(1):4-10.