Article: EPA-0643
Topic: E07 - e-Poster Oral Session 07: Neurobiology, Bipolar Disorders and psychopathology

EFFECT OF AGOMELATINE ON REWARD AND PUNISHMENT PROCESSING IN A PROBABILISTIC REVERSAL LEARNING TASK IN MICE; ROLE OF ITS MT1/MT2 AGONIST AND 5HT2C ANTAGONIST PROPERTIES

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Introduction: Reward and punishment alterations are observed in depressed patients (Taylor Tavares et al., Neuroimage, 2008). Reward hypo-sensitivity and punishment hyper-sensitivity can be studied in humans and animals using operant tasks, such as the probabilistic reversal learning (PRL) task (Ineichen et al., Neuropharmacology, 2012).

Aims: To determine the effects of the new antidepressant agomelatine (AGO), a MT_1/MT_2 melatonergic receptor agonist and 5-HT_{2C} receptor antagonist on reward and punishment processing as well as to evaluate its mechanism of action.

Methods: Mice learned spatial discrimination for sucrose-pellet reward in an operant apparatus. In the PRL task, mice were assessed on reward-stay, negative feedback sensitivity (NFS) and reversals completed. Using latin-square designs, agomelatine (AGO 10 or 25 mg/kg), melatonin (MT 10 or 25 mg/kg), the 5-HT_{2C} antagonist S 32006 (2.5 or 5 mg/kg) or vehicle (VEH) were administered acutely i.p. An additional group of mice was treated acutely i.p. with the $MT_{1/2}$ antagonist S 22153 (20 mg/kg) + VEH or S 22153 (20 mg/kg) + AGO (25 mg/kg).

Results: Data underwent a median-split (high vs low performers) according to PRL behaviour under VEH. In low-performing mice specifically, AGO at 25 mg/kg increased reward-stay, decreased NFS and increased reversals completed, relative to VEH. There were no effects of MT or S 32006. Agomelatine effects were counteracted by prior administration of the $MT_{1/2}$ antagonist S 22153.

Conclusions: Agomelatine acutely is able to increase reward sensitivity and decrease punishment sensitivity in mice. The results suggest a potential synergy between its melatonergic agonist and 5-HT_{2C} antagonist properties.

https://doi.org/10.1016/S0924-9338(14)78017-4 Published online by Cambridge University Press