INTRODUCTION

Agomelatine is a novel antidepressant drug with melatonergic agonist and 5-HT2C receptor antagonist properties, displaying antidepressant and anxiolytic properties in several animal paradigms and in clinics. Preclinical data have also demonstrated that agomelatine increases cell proliferation in the dentate gyrus of the hippocampus. Indeed, chronic treatment with agomelatine in the rat increased both the number of BrdU-labeled cells in the subgranular layer (SGZ) and the survival of newly formed neurons in the dentate gyrus. Recently, Santarelli and colleagues used a radiological method (X-irradiation) to demonstrate that the behavioral effects of chronic selective serotonin reuptake inhibitors (SSRIs) and tricyclics (TCAs) in the novelty-suppressed feeding test (NSF) required hippocampal neurogenesis.

Based on these findings we decided to test agomelatine in the NSF in mice and to assess whether hippocampal neurogenesis is also modulated by agomelatine.

MATERIALS AND METHODS

Animals: Male 129SvEvTac from Taconic Farms, 8-10 weeks old, were used in these experiments.

Drugs and treatment: Mice were treated intraperitoneally at 5 pm (1 hour before the start of dark phase, 6 pm), once a day for 27 days with agomelatine (S20098) (40 mg/kg/day), fluoxetine (18 mg/kg/day), or the corresponding vehicle in Sham and X-ray mice. Fluoxetine and agomelatine were dissolved in saline and hydroxy-ethyl-cellulose (HEC 1%) respectively.

Irradiation: Mice were anesthetized with ketamine and xylazine, placed in a stereotaxic frame and exposed to cranial irradiation using a Siemens Stabilopan X-ray system operated at 300 kVp and 20mA. Mice received 3 doses of 5Gy on days 1, 4, and 8 of treatment. Sham animals had the same procedures without irradiation.

Immunohistochemistry: To assess the effects of agomelatine or fluoxetine treatments on neurogenesis in mice, irradiated or not, BrdU (150 mg/kg ip dissolved in saline) was administered to mice, 2 hours before sacrifice on day 29 for BrdU-positive cells counting.

In situ hybridization: In situ hybridization was performed as previously described.

Behavior: The NSF is a conflict test that elicits competing motivations; the drive to eat and explore, the fear of venturing into the center of brightly lit arena. The test was done during 10 minutes on day 28, 21 hours after the last drug administration. 24 hours prior to the test, food was removed. Latency to begin eating was used as an index of anxiety behavior. After the test, mice were tranferred to their home cage and their food consumption was measured during the next 5 minutes.

RESULTS

Agomelatine and fluoxetine decreased the latency to feed in the NSF. The effects of agomelatine were greater than those of fluoxetine. Neither drug showed any effects in X-rayed mice, after the last drug administration. 24 hours prior to the test, food was removed. Latency to begin eating was used as an index of anxiety behavior. After the test, mice were tranferred to their home cage and their food consumption was measured during the next 5 minutes.

REFERENCES

5. 1 - EA 3544, Université Paris-Sud XI, Chatenay-Malabry, France; 2 - Institut de Recherches Internationales Servier, Courbevoie, France; 3 - Neurosciences and Psychiatry, Columbia University, New York, NY.