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Antidepressant-like activity of agomelatine in the mouse unpredictable chronic mild stressed model

O Mutlu[1], G Ulak[1], E Gumuslu[3], I Celikyurt[1], F Akar[1], E Bektas[1], T Demirtas[1], HM Kir[2], M Musul[2], F Erden[1]. *[1]Kocaeli University, Pharmacology/41380, Turkey, [2]Kocaeli University, Biochemistry/41380, Turkey, [3]Kocaeli University, Genetics/41380, Turkey*

Depression is one of the most debilitating and common psychiatric diseases. Unpredictable chronic mild stres (ucms), a promising and valuable animal model of depression which shows similar features to the depressive symptoms seen in human beings (Willner, 1997). Agomelatine, a novel antidepressant with established clinical efficacy, acts as an agonist of melatonergic mt_1 and mt_2 receptors and as an antagonist of 5-ht_{2C} receptors (Millan et al., 2003). The present study was undertaken to investigate whether chronic agomelatine treatment would block ucms-induced depression-like behavior in mice compared to the selective 5-ht reuptake inhibitor (ssrı) fluoxetine and endogenous melatonergic agonist melatonin. Male inbred 30-40 g male balb/c mice were subjected to different kinds of stressors several times a day for 7 weeks. Animals were treated intraperitoneally with agomelatin (10 mg/kg), melatonin (10 mg/kg), fluoxetine (15 mg/kg) or vehicle for 5 weeks (n= 18 per group). Mice were randomly assigned to one of the 8 following experimental groups: non stressed vehicle (nc), non stressed fluoxetine (nf), non stressed melatonin (nm) , non stressed agomelatin (na), ucms-ed vehicle (sc), ucms-ed fluoxetine (sf), ucms-ed melatonin (sm), ucms-ed agomelatin (sa). One-way Anova post-hoc Tukey's test was used for the comparison of groups. To determine the effects of ucms regimen and drug treatment, we examined the state of the coat in mice and performed behavioral tests such as splash, resident intruder, tail suspension and forced swimming tests respectively. The open field test was also performed to measure the locomotor activity of drugs.The results of this study revealed that: (1)A significant difference between the coat state score of non-stressed (0.12±0.08) and ucms-exposed group (3.81±0.09) was observed ($p<0.001$). Agomelatine, significantly reversed the ucms-induced degradation in the coat state (0.43±0.23) ; the magnitude was comparable to melatonin (0.6±0.27) and fluoxetine (1.37±0.39) ($p<0.001$) (2) There was no significant difference between the body weight of the animals at the end of ucms regimen (nc=36.87±1.77; sc=33.5±0.82; sf=36.37±1.84; sm=34. 62±1.03; sa=34.5±1.16). The locomotor activity experiment showed a lack of stimulant or depressant effect of the tested antidepressants after repeated administration (nc=1618.22±38.86; sc=1890.01± 68.55; sf=1623.69± 111.44; sm=1717.49± 59.62; sa=1734.07± 46.26 (3) All drugs tested blocked the stress-induced deficit in total number of grooming in splash test (nc=20.5±1.45; sc=8.62±1.38; sf=26.12±2.34; sm=24.12±1.72; sa=26.37±1.98) ($p<0.001$), decreased the attack frequency in resident intruder test (nc=1.25±0.83; sc=23.37±2.93; sf=0.37±0.26; sm=6.5±2.25; sa=2.87±1 .24) ($p<0.001$), reduced the immobility time in tail suspension test (nc=60.75±9.39; sc=187.12±9.61; sf=79.62±7.66; sm=65±13.25; sa=43.87±6.95) ($p<0.001$) and forced swimming test (nc=207.37±13.31; sc=269.42±4.42; sf=198.87±7.86; sm=216.87±13.25; sa=215.28±14.05) ($p<0.05$). (4) All drugs decreased enhanced levels of plasma acth (nc=46.18±8.47; sc=213.66±26.66; sf=117.33±10. 25; sm=107.83±14.95; sa=122.35±15.80) ($p<0.01$); cortisol (nc=0.59±0.05; sc=2.07±0.65; sf=0.29±0.05; sm=0.71±0.18; sa=0.36±0.03) ($p<0.01$); il-6 (nc=171.06±12.32; sc=1977.55±714.97; sf=262.31±69.75; sm=49.55±18.05; sa=76.66±28) ($p<0.001$) and Tnf-α levels (nc=37.68±11.83; sc=101.73±24.24; sf=40.54±8.45; sm=43.12±1.98; sa=39.21±4.71) ($p<0.05$) in stressed mice.

The results of this study support the assumption that agomelatine, with a novel mode of action and a favourable clinical safety and tolerability profile is effective as much as fluoxetine for the treatment of depression.

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