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Effects of agomelatine, a melatonergic receptor agonist, on pentylenetetrazole-induced kindling, kindling-associated oxidative stress, depression and impairment of spatial memory in mice and possible modulation of its actions by luzindole and 1-(m-chlorophenyl) piperazine

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Introduction: In view of well-evidenced antiepileptic effects of melatonin and few reports of anticonvulsant action of agomelatine, the present study investigated whether agomelatine protects against pentylenetetrazole (PTZ)-induced kindling in mice and kindling associated oxidative stress, depression and impairment of spatial memory. In order to explore whether effects are mediated by melatonergic or serotonergic mechanisms, 1-(m-chlorophenyl) piperazine (mCPP), a selective 5HT2c receptor agonist and luzindole, a melatonin receptor antagonist (with greater selectivity for MT2 as compared to MT1 receptors), were taken as pharmacological tools. In view of few hepatotoxic reports on agomelatine, the study evaluated effects on hepatic enzyme levels.

Method: Swiss strain albino male mice aged 5-6 weeks were injected with PTZ (25mg/kg,ip) once every two days for 5 weeks to induce kindling. The effects of agomelatine (10mg/kg, po) alone and in combination with luzindole (2.5 mg/kg, ip) or mCPP (7 mg/kg, ip) on the seizure severity during induction and % incidence of animals kindled at the end of 5 weeks was recorded. The modified forced swim test was used for studying depression-like behaviour while spontaneous alternation behaviour (SAB) was used for the studying effects on spatial memory. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations, cortical and hippocampal malondialdehyde and reduced glutathione were estimated. Seizure severity was analyzed by Kruskal-Wallis one-way analysis by ranks test. For incidence % of seizures and alternation, Fisher's exact probability test was used. All other data was analyzed by ANOVA followed by Tukey-Kramer multiple comparison tests. P-values <0.05 were considered to be significant.

Results: Agomelatine 10mg/kg, p.o effectively protected the animals against development of kindling as indicated by reduced seizure severity and decreased % incidence ($p<0.01$, $n=5$). The concurrent administration of agomelatine with mCPP had no effects on % incidence or seizure severity while that with luzindole significantly reversed its protective effects ($p<0.01$). Kindling was associated with increase in immobility time, decrease in swimming and climbing behaviour ($p<0.001$). Agomelatine treatment reversed the effects on behavioural despair especially on immobility and swimming time ($p<0.001$). It also reversed the reduction of locomotor activity and % alternation induced by PTZ kindling. Further, agomelatine normalized the cortical and hippocampal malondialdehyde levels and reduced GSH levels ($p<0.001$) and elevated liver enzymes following PTZ-kindling.

Conclusions: Agomelatine delayed the development of PTZ-kindling and reduced the incidence of seizures. Luzindole reversed the protective effects of agomelatine while mCPP failed to show such a reversal indicating melatonergic (and not serotonergic) mechanisms in the observed effects. Agomelatine also showed antioxidant effects that can partially contribute to its anticonvulsant action. In addition, it alleviated PTZ-kindling associated behavioural despair and favourably modulated liver enzymes. Its effects on improvement of kindling-associated spatial memory could possibly be related to its effects on locomotor activity. Agomelatine, thus, could be explored as an adjunct to antiepileptic drugs for seizure control and for alleviating epilepsy associated depression.