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Neuropharmacological studies of novel melatonin derivatives

The majority of available literature on experimental animals revealed that melatonin has anticonvulsant action in acute seizures tests with different mechanism of action. An important advantage of melatonin as an add-on option in a therapy of epilepsy is associated with its low toxicity, antioxidant activity as well as its ability to synchronize disturbed circadian rhythms in epileptic patients. A series of melatonin analogues, containing indole scaffold, were synthesized and their anticonvulsant activity was tested on ICR mice by measuring the time of three different seizure phases (myoclonic, clonic and tonic) induced by intravenous infusion of pentylenetetrazol (PTZ). The novel melatonin derivatives were synthesized according to the classical method by condensation of hydrazones with 5-methoxyindole-3-carboxaldehyde or 5-benzyloxyindole-3-carboxaldehyde. The hydrazone-hydrazones with indole moieties were purified by recrystallization and the molecular weights were determined, using ES-MS. The compounds were injected intraperitoneally at doses of 30, 60 and 100 mg/kg 30 min before PTZ. The most potent compounds, with significantly increased thresholds for myoclonic, clonic and tonic seizures compared to vehicle were the derivatives with 2-thienyl and p-Cl-phenyl fragments at a dose of 60 mg/kg, which effects was comparable to that of melatonin at the same dose of 60 mg/kg, used as a positive control. None of the compounds displayed neurotoxicity in the rota-rod test. *In silico* assessment of their BBB permeability indicated them as CNS active agents. Molecular docking was performed into a human gamma-aminobutyric acid (GABA_A) receptor and depicted good binding properties of melatonin derivatives, considered in this study. Based on anticonvulsant screening results, these newly synthesized melatonin derivatives will be explored in other seizure tests with different mechanism of action as well as in models of epilepsy.

Biography

Jana Tchekalarova has completed her PhD in Pharmacology in 2004 from Institute of Physiology, BAS. She has 22 years of research experience. She is currently working as an Associate Professor at the Institute of Neurobiology, BAS and as the Head of Behavioral Neurobiology Dept. She is an Adjunct Professor at the Section of Biochem., Physiology and Pathophysiology in the Med. Dept. of Sofia University. According to Mendeley profile her h-index=12, publications 51 with IF; citations=385. She has more than 500 citations. She has been serving as an Editorial Board Member of *Drug Development Research*, *Journal of Neurological Disorders and Stroke* and Asian Council of Sci Editors.

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