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Study of antinociceptive and sedation activity of a novel class of vesicular monoamine transporter inhibitors in rats

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The pharmacological characteristics of a novel vesicular monoamine transporter (VMAT) inhibitor, '4-phenyl-1-(2-phenyl-allyl)pyridinium bromide', has been explored in this study to understand the *in vivo* mechanisms of action of APP-MPP^+ conjugates. A convergence synthesis of 4-phenylpyridine and α-(bromo)methylstyrene was carried out and finally combined to yield the APP-MPP^+ conjugated inhibitor.

Male albino rats were orally administered with different doses (12.5, 25, 50 mg/kg) of the drug and the reaction times on hot-plate and tail flick tests were recorded. In the hot-plate test significant ($p < 0.01$) increment in the reaction time of rats at 1 h and 2 h was evident, while the tail-flick test failed to induce a significant prolongation. The antinociceptive effect (analgesic) was dose dependent, with an EC_{50} value of 23.5 mg/kg. In the hole-board test, the mid dose of the drug significantly impaired the number of crossings (by 48%, $p < 0.005$), rearings (by 25%, $p < 0.02$), head dippings (by 40%, $p < 0.02$) and the dipping time (by 64%, $p < 0.005$). These effects were also dose dependent. These effects were genuine and not false positive results arising from impairment of muscle strength and coordination (as judged by bar and bridge tests respectively), or hypothermia (as judged by rectal temperatures). Membrane stabilization effect was absent under the doses tested (0.01, 0.02, 0.04 mg/mL). The drug induced antinociception was not blocked by atropine, but was blocked by metoclopramide, indicating a D_2 receptor mediation of action. These results correlate with previous findings that APP-MPP^+ conjugates are monoamine transporter inhibitors. This possibly indicates the inhibition of the dopamine transporter (DAT) and to an increase of dopamine in the synaptic cleft, inducing analgesia. Even the high dose of the drug was well tolerated. Since this compound has promising sedative and analgesic potentials, it is concluded that APP-MPP^+ compounds could be developed in to a novel class of drugs to effectively treat various neurological and physiological disorders, provided that neurotoxicity is ruled out.

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