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Poster presentation

Behavioural and antioxidant activity of a tosylbenz[g]indolamine derivative. A proposed better profile for a potential antipsychotic agent

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Background

It is known that tardive dyskinesia (TD) is a major limitation of chronic antipsychotic drug therapy at least with older (typical) antipsychotics. Atypical antipsychotics possess a lower extrapyramidal side effects liability. However, they brought about various side effects such as weight gain, hyperglycemia, cholesterol level elevation, and QT interval prolongation. Therefore, it becomes interesting to design compounds that maintain antipsychotic efficacy and simultaneously could be free of TD risk. In a previous study we have shown that an indolamine molecule (PBIA, Figure 1) expresses a moderate binding affinity at the dopamine D_2 and serotonin 5-HT_{1A} receptors in in vitro competition binding assays. In the present work, we tested its p-toluenesulfonyl derivative (TPBIA) for behavioral effects in rats, related to interactions with central dopamine receptors and its antioxidant activity, since free radical processes are implicated in the pathophysiology of a number of CNS disorders, including TD.

Material and Methods

The experimental animals (adult male Fischer-344 rats) were grouped as: i) Untreated rats: TPBIA was administered i.p. in various doses and immediately afterwards the rats were placed individually in the activity cage and their motor behaviour was recorded for the next 30 min, ii) Apomorphine-treated rats: the motor activity was measured as described above in the rats treated with apomorphine (1 mg kg^{-1}, i.p.) 10 min after the administration of TPBIA. The antioxidant potential of TPBIA was investigated in the model of in vitro non enzymatic lipid peroxidation.

Results

It was found that: i) In non-pretreated rats, TPBIA reduces the activity by 39 and 82% respectively, ii) In apomorphine pretreated rats, TPBIA (80 μmol/kg) reverses the hyperactivity and stereotype behaviour induced by apomorphine. Also, it was found that TPBIA completely inhibits the peroxidation of rat liver microsome preparations at concentrations of 0.5, 0.25 and 0.1 mM.

Discussion

TPBIA might have therapeutic potential in the treatment of psychosis, due to its dopamine antagonistic activity in the central nervous system. In addition, its antioxidant effects is a desirable property, since tardive dyskinesia – a neuroleptics' side effect – has been attributed, at least in part, to oxidative stress.

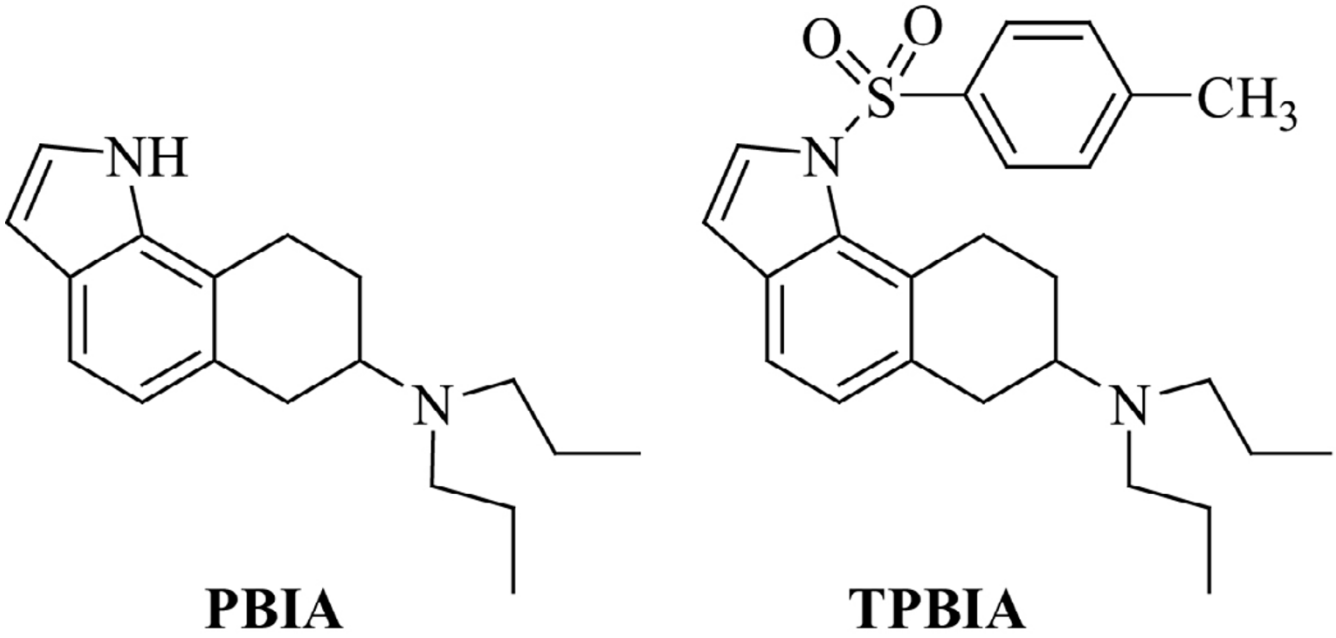

Figure 1
Indolamine molecule (PBIA) and its p-toluenesulfonyl derivative (TPBIA).