Design of GABA uptake inhibitors: synthesis and anticonvulsant properties

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Background and Objective: Epilepsy is the most common primary neurological disorder known, affecting 0.4-0.8% of the population and up to 50 million people worldwide.[1] 4-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain plays an important role in the etiology and control of epilepsy by mediating the inhibition processes of epilepsy.[2] The inability of GABA to cross the blood-brain barrier has directed research to the development of various analogues of this neurotransmitter. The present study is aimed at design, synthesis and evaluation of lipophilic analogues of GABA as effective GABA-reuptake inhibitors and with a wide spectrum of activity in various animal models of seizure.

Methods: The structural analogues of GABA (RJ 1-RJ 10) were designed based on the following pharmacophoric requirements for action as inhibitors of the GABA transporter (GAT)-1: (i) an amine functional group (preferably a secondary amine), (ii) a lipophilic binding region (preferably aromatic), (iii) a carboxylic acid functionality and (iv) an electron-rich functionality (double bond or oxygen) located between the amine and the lipophilic region. The synthesized compounds were evaluated for their anticonvulsant efficacy in the maximal electroshock seizure threshold test (MES) and subcutaneous pentylenetetrazole (scPTZ)-induced seizure test, as well as in the subcutaneous picrotoxin-induced (scPIC) chemoshock model to ascertain the GABAergic mechanism. In order to ascertain the GABA regulation mechanism, one of the compounds was tested *in vitro* using [^{3}H]-GABA uptake inhibition assay and the K_i value was determined.

Results: Most of the synthesized compounds showed promising anticonvulsant activity (at a dose level of 30mg/kg) in both the primary *in vivo* animal models. The scPIC study results showed the definite involvement of the GABAergic pathway in the mechanism of action of the compounds. Using rat brain synaptosomes, the [^{3}H]-GABA uptake inhibition of one representative compound (RJ 7) was determined and was found to inhibit the uptake in neuronal (IC_{50} = 50 μmol) and glial (IC_{50} = 22 μmol) cell cultures. Tiagabine was used as a standard for comparison, which inhibited GABA uptake in neuronal and glial cell cultures with IC_{50} of 446 nmol and 128 nmol respectively.

Conclusion: Taken together the experimental results, it is observed that these novel compounds exhibited protection in MES, scPTZ and scPIC models and that they could be considered as effective GABA uptake inhibitors with the pharmacophoric features conforming to the hypothetic prerequisites.

References

1. McNamara JO. Emerging insights into the genesis of epilepsy. *Nature* 1999; 339: A15-22.
2. Meldrum BS. Epilepsy and gamma-aminobutyric acid-mediated inhibition. *Int Rev Neurobiol* 1975; 17: 1-36.