2-AMINOBENZENSULFONAMIDES DERIVATIVES AS ALLOSTERIC MODULATORS OF AMPA/KAINATE RECEPTORS

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Recent studies indicate that compounds that reduce the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor desensitization could improve impaired synaptic functions associated with learning and cognition pathology and can be useful in the treatment of attention disorders in children as well as in senile dementias, including early stages of Alzheimer disease. Among these compounds, (±)IDRA21 (7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide) has attracted particular interest for its ability to act as cognitive enhancing agent in normal young and aged rhesus monkeys when given orally in low (0,5-10 mg/Kg) doses. Despite the high potency in modulating AMPA receptor function in vivo of (±)IDRA21, its potency in vitro is low with an EC_{50} close to 100 μM. Since (±)IDRA21 has been administered orally in the in vivo pharmacological tests, studies on the stability of the drug in acidic condition similar to that of stomach are clearly matter of interest. Hydrolysis of IDRA21 at different pH and temperature was studied by a chromatographic procedure. The results have been shown that IDRA21 undergoes rapid hydrolysis in acidic solution to 2-amino-5-chlorobenzensulfonamide and acetaldehyde.

Moreover microdialysis experiments have been demonstrated that in vivo IDRA21 hydrolyses to give 2-amino-5-chlorobenzensulfonamide which was present at high levels in the brain for at least six hours after oral administration of IDRA21 itself. Subsequently electrophysiological experiments have been demonstrated that 2-amino-5-chlorobenzensulfonamide posses in vitro a biological activity similar to that of IDRA21.

Taking 2-amino-5-chlorobenzenesulfonamide as lead compound, a series of 2-aminobenzensulfonamides with different substituent at benzene ring and amino groups has been prepared and studied for their activity as allosteric modulators of kainate-activated currents in primary cultures of cerebellar granule neurons.

Some terms were powerful potentiators of kainate-activated currents, with activity close to that of IDRA21. These compounds could be good candidates as new therapeutic agents for the treatment of cognitive deficits.