ACEA 1021: Flip or Flop?

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ABSTRACT

Inasmuch as glutamate is the main excitatory neurotransmitter in the central nervous system, strategies aimed at counteracting glutamate excitotoxicity, which is at least partially involved in many acute neurologic, chronic neurodegenerative and psychiatric diseases, are challenging. Blockade of the NMDA receptor was identified as one way of achieving selective antagonism and overcoming glutamate neurotoxicity, yet not without liabilities. Glycine site antagonism of the NMDA receptor in 1987 offered a significant advance in blocking this receptor because such drugs were shown to lack most of the side effects, such as memory impairment, ataxia, lack of motor coordination and psychotomimetic effects, which accompanied competitive and non-competitive NMDA receptor antagonists. To date, much has been done to improve the structure-activity relationship (SAR) of compounds resulting in the synthesis of ACEA 1021. It is unclear, however, whether further chemical substitutions will lead to an improved compound. Many studies have been performed with ACEA 1021 and although there are much in vitro and in vivo data to support its neuroprotective effects and improved safety profile, there is very little published information regarding its clinical pharmacology. In order to properly evaluate the true potential for ACEA 1021 in acute and chronic CNS disorders additional longer term safety and efficacy data in humans are needed.