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Glycine$_B$ recognition site of NMDA receptors and its antagonists

Introduction

It is now generally agreed that glutamate is the major fast excitatory neurotransmitter in the CNS. Malfunctioning of glutamatergic neurotransmission has been implicated in a wide variety of neurological diseases such as ischaemia during stroke and trauma, Parkinson's and Huntington's disease, dementia, ALS, AIDS-neurodegeneration, Tourette's syndrome, epilepsy, schizophrenia, anxiety, depression, chronic pain and tardive dyskinesia. As such, there is a great deal of interest in the development of glutamate antagonists for therapeutic use. Glutamate activates three major types of ionotropic receptor, namely α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and N-methyl-D-aspartate (NMDA) and several types of metabotropic receptors. Recently attention has focused on the development of NMDA antagonists acting at the glycine site (glycine$_B$) since a favourable therapeutic profile for such agents has been suggested (Danysz et al., 1998).

Glycine is a coagonist at the NMDA receptors showing complex interactions with other recognition sites of this receptor complex (Parsons et al., 1998). Better understanding of these basic determinants is a prerequisite for rational development of better, safer drugs. Until now, only a few glycine$_B$ antagonists with favourable penetration to the brain have been introduced (Parsons et al., 1998).

One of the groups of such agents was developed by Merz+Co. They show potent activity *in vivo* as evidenced by inhibition of convulsions and of responses to ionophoretically applied NMDA in the spinal cord (McClean et al., 1998). These agents also show antinociceptive activity which is more pronounced in hyperalgesic animals (McClean et al., 1998). Merz glycine$_B$ antagonists also are potent neuroprotectants as evidenced by inhibition of neurodegeneration of NBM after local application of NMDA (Wenk et al., 1998). This effect is seen both after pre- and post-treatment.

One of the possible therapeutic uses of glycine$_B$ antagonists includes Parkinson's disease. In fact glycine$_B$ antagonists produced only weak or no stereotypy and attenuate haloperidol-induced catalepsy (Kretschmer, 1998), although their effect in other models of Parkinsonism is weak to none (Danysz et al., 1998).

More systematic studies on glycine$_B$ antagonists in animal models indicate that they might find therapeutic use as neuroprotectants, in drug abuse and inhibition of drug tolerance (Danysz et al., 1998). The most pronounced side effect seen is ataxia, though no indications of psychotomimetic potential have been detected.

After the recent introduction of systemically available glycine$_B$ antagonists, the coming years should reveal whether they indeed represent attractive agents for drug development.

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