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Chapter III

Uncompetitive NMDA receptor antagonists – Is low affinity better?

Introduction

NMDA receptor antagonists have a potentially wide spectrum of therapeutic applications ranging from symptomatic treatment of Parkinson's disease, Alzheimer's disease, migraine, and drug abuse to neuroprotection in a number of diseases, just to mention a few (Parsons et al., 1998). Inhibition of this receptor type can be achieved through interaction with any of several recognition sites (competitive to glutamate, non-competitive glycine site, polyamine site, redox site) and a use-dependent channel block. However, in spite of extensive research for the last 10 years, none of the specifically designed agents has entered clinical use because of unfavourable side-effect profiles and/or lack of efficacy (stroke/trauma trials mainly, Lee et al., 1999). Therefore the question arises whether inhibition of NMDA receptors is a valid approach. To tackle this one should bear in mind that several agents that are already in clinical use have been found years after they introduction to clinical practice**,** to inhibit NMDA receptors. Interestingly all of them are channel blockers (memantine, amantadine, dextromethorphan, mepyramine, desipramine, orphenadrine; Parsons et al., 1998). This proof of principle is however faced with a serious drawback since in fact the use of other channel blockers such as PCP or dizocilpine has been connected with serious side effects and in the former case with significant abuse potential and psychotomimetic activity. This apparent paradox can be explained by a different mode of action – namely better tolerated agents show moderate to low affinity (high nM, low μM) as compared to the very high affinity displayed by PCP or dizocilpine (low nM range) (Rogawski, 1993). There are several other determinants of good tolerability of NMDA channel blockers like high voltage dependency, degree of partial trapping and other factors that are discussed in the following articles.

Hence, the general question: "Can NMDA receptor antagonist**s** be applied in the clinic?", has definitely already been answered "yes". Learning why some are better is a key step for development of new, even more effective and safer agents. The aim of the present session was to point out the features of NMDA channel blockers that are determinants of their efficacy and/or safety.

From the basic science point of view it is very interesting that substances acting, apparently at the same site, show such different pharmacological

profiles. Elucidation of this aspect should lead to a better understanding of basic biophysical properties of channel function and its physiological mode of functioning.

It has already become a tradition of the Amino Acids Congress to publish papers summarizing oral presentations. This approach clearly broadens the group of potential addressees. The participants of the symposium "*Uncompetitive NMDA receptor antagonists – is low affinity better?* "have written summaries of their presentations focusing on new agents under development and/or analysis of general features crucial for good clinical tolerability of such agents.

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