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Low affinity use-dependent NMDA receptor antagonists show promise for clinical development

Review Article

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Summary. The success of the low affinity use-dependent NMDA receptor antagonists to reach clinical trials can be readily attributed to their wider margins of safety and lack of neurotoxicity at higher doses. Several mechanistic differences distinguish the low affinity from the high affinity use-dependent antagonists: 1) Differential regional affinities for the various NMDA receptor subtypes; 2) The static receptor blockade due to the faster on/off rate receptor kinetics which limit, but do not totally prevent the amount of Ca^{+2} entry into the cell during glutamate-induced depolarization; and 3) Rapid egress of the compounds from the ion channel during recovery resulting in less membrane trapping between transmission pulses. Advanced clinical trials are in progress for the following indications: epilepsy, stroke, head trauma, tardive dyskinesia, pain plus Parkinson's, Huntington's and Alzheimer's diseases.

Keywords: Amino acids – NMDA – Low affinity use-dependent antagonists – Clinical status – Epilepsy – Stroke – Head trauma – Neurodegeneration

Mechanisms of action

Despite the unfavorable literature describing untoward side effects for competitive and high affinity use-dependent NMDA receptor antagonists, one group of compounds has made it successfully into the clinic with some compounds already marketed (see below). What characteristics distinguish low affinity use-dependent NMDA receptor antagonists from their high affinity counterparts? Low affinity antagonists exhibit the following –

1) Wide separation between doses producing efficacy to side effects which include: phencyclidine-like abuse liability, motor incoordination, disruption of learning and memory, and transient neuronal vacuoles in the cingulate and retrosplenal cortices (Palmer and Hutchison, 1997; Palmer et al., 1999; Parsons et al., 1998, 1999; Rogawski, 1992).

2) Affinity at the open channel ionic site is in the μM range, in contrast high affinity compounds exhibit low nM affinity (Mueller, 1999; Palmer et al., 1999; Parsons et al., 1998; Rogawski, 1992).
3) The on/off rate kinetics for the low affinity compounds are considerably more rapid, especially the off rate (Black et al., 1996; Monaghan and Larson, 1997; Mealing et al., 1999; Parsons et al., 1998; Rogawski, 1992). In this regard NMDA-triggered $[Ca^{+2}_i]$ entry into neurons can be limited but not completely prevented by the low affinity antagonists allowing the neuron to maintain critical calcium homeostasis (Black et al., 1996). Therefore less drug is trapped within the receptor channel between NMDA receptor-mediated activity (Mealing et al., 1999; Parsons et al., 1998). The blockage of the receptor is dynamic and not the sustained, complete tonic block associated with the high affinity antagonists (Parsons et al., 1998).
4) Low affinity antagonists are preferentially localized in the hind brain (cerebellum and mesencephalon), whereas the high affinity compounds are more preferentially distributed to forebrain structures (Porter et al., 1995).
5) Low affinity compounds display less inhibition of NMDA NR1/NR2a receptor subtypes with slightly more preferential affinities for NR1/NR2c & b subtypes (Monaghan and Larson, 1997; Parsons et al., 1998).
6) Chronic administration is not associated with neurotoxicity (Palmer et al., 1999).

Specific low affinity use-dependent NMDA receptor antagonists have been shown to possess additional mechanisms of action. For example, felbamate potentiates GABAa receptors, remacemide hydrochloride and ADCI are Na^+ channel blockers, AR-R15896AR and amantadine possess affinity at sigma receptors, while amantadine and memantine block nicotinic receptors (See Palmer and Hutchison, 1997; Palmer et al., 1999; Parsons et al., 1998; Rogawski, 1992).

Epilepsy

Low affinity use-dependent NMDA antagonists inhibit seizures in rodents elicited by maximal electroshock (MES), an event associated with fast Na^+ channel activity. In addition, convulsions and mortality following administration of NMDA are prevented. It is of interest that only four low affinity use-dependent NMDA antagonists have been tested in epileptic patients, namely dextromethorphan (Phase II, dropped because of sedation), ADCI (Phase I, unforeseen long term toxicology in animals), felbamate (marketed, but use limited because of potential aplastic anemia) and remacemide hydrochloride (ongoing advanced phase III trials) (Palmer and Hutchison, 1997; Parsons et al., 1998, 1999; Rogawski, 1992). Novel, safe compounds are needed to treat epilepsy. Why the lack of interest for clinical trials? There are several reasons:

1) return on investment – the market for treatment of stroke, head trauma and/or neurodegenerative diseases is potentially unlimited,

2) high doses are proconvulsant and might cause abuse liability,
3) questionable efficacy in models of kindling and status epilepticus. Low affinity NMDA antagonists inhibit development of kindling due to subthreshold stimulation from a specific brain locus (hippocampus or amygdala) but are not active in more generalized kindling models. Moreover, some studies indicate the compounds prolong a kindled- or status-induced state (Palmer et al., 1999, Parsons et al., 1998; Rogawski, 1992). Interestingly, Remacemide Hydrochloride has been show to be effective in drug-resistant patients with complex partial seizures (Palmer and Hutchison, 1997) – the question remains whether kindling is a suitable model for complex partial seizures?
4) Use in pediatrics – specific subtypes of NMDA receptors are associated with establishment of proper synaptic connectivity in the infant brain plus the inherent potential problems associated with learning (Parsons et al., 1998);
5) Costs of chronic toxicology studies and novel compounds may produce novel, unforeseen toxicities e.g., transient vacuoles, neuronal death.

Stroke

Stroke has been an area of intense investigation and clinical trials for the low affinity use-dependent NMDA receptor antagonists are in progress. In laboratory investigations low affinity antagonists prevent long-term neuronal damage in models of transient and permanent focal ischemia; protection is observed in both lissencephalic and/or gyrencephalic animals. Remacemide Hydrochloride (Palmer and Hutchison, 1997), HU-211 (see: Parsons et al., 1998), NPS-1506 (Mueller, 1998) and AR-R 15896AR (Palmer et al., 1999) have all reached Phase II trials in patients with acute focal ischemia. Analogous conclusions with clinical evaluations in patients with stroke are difficult to compare with the rigidly controlled animal studies. To be effective, NMDA antagonists must be administered shortly after a stroke; whereas, depending upon the severity of the attack, patients arrive at the emergency room at various times ranging up to 48 hours post-ictus. Another problem is patient classification. In order to demonstrate statistical effectiveness of a compound in animal studies, a moderate to severe stroke must be administered to the animal. It's doubtful if the drugs would ever show effectiveness in patients with mild stroke. Better, more accurate clinical measures of drug efficacy must be developed. There is uncertainty as to the duration of treatment; clinical trials typically use treatment periods of 24–72 hours after the patient is admitted. Longer treatment may be better.

Head trauma

Low affinity use dependent NMDA receptor antagonists (HU-211, dextromethorphan, memantine + flunarizine, NPS-1506, remacemide hydrochloride) show varying degrees of efficacy in animal models of head

trauma, brain edema and subarachnoid hemorrhage (Mueller, 1999; Palmer and Hutchison, 1997; Parsons et al., 1998). Currently HU-211 is in Phase III clinical trials and NPS 1506 is under consideration for an early Phase II study (Mueller, 1999; Parsons et al., 1998). Again the major questions are how long after ictus is initial treatment effective and proper patient selection?

Neurodegeneration

Excitatory amino acid-induced neuronal death may be rapid (e.g., stroke, severe seizures, anoxia) or slow in onset. In the latter case, processes of neurodegeneration that evolve slowly over time might be prevented with a safe acting NMDA receptor antagonist, events supported by animal investigations – efficacy reported for memantine, amantadine, dextromethorphan (Parsons et al., 1998), remacemide hydrochloride (Palmer and Hutchison, 1997) and AR-R 15896AR (Palmer et al., 1999). Therefore it is not surprising that low affinity NMDA receptor antagonists were found to be useful in the treatment of Parkinson's disease (see below). Moreover, intensive Phase II/III clinical trials are ongoing with memantine in various types of dementia including Alzheimer's Disease (Parsons et al., 1998). A phase II/III trial is underway with Remacemide Hydrochloride in patients with Huntington's Disease (Palmer and Hutchison, 1997, unpublished).

Clinical status – Summary (see: Mueller, 1999; Palmer and Hutchison, 1997; Palmer et al., 1999; Parsons et al., 1998)

- *Epilepsy* – felbamate (marketed, recommended for Lennox-Gastaut syndrome), remacemide hydrochloride (Phase III), ADCI (Phase I, discontinued), dextromethorphan (Phase II discontinued).
- *Stroke* – NPS 1506 (Phase II), HU-211 (Phase II), AR-R 15896AR (Phase II).
- *Head trauma* – HU-211 (Phase III), NPS-1506 (Phase II planned).
- *Parkinson's disease* – amantadine (marketed), memantine (marketed for associated spasticity), budipine (marketed), remacemide hydrochloride (Phase II use in conjunction with l-dopa).
- *Huntington's disease* – remacemide hydrochloride (Phase II/III).
- *Alzheimer's disease / dementia* – memantine (several Phase II/III trials), remacemide hydrochloride (early Phase II).
- *Tardive dyskinesia* – amantadine (marketed).
- *Pain* – dextromethorphan (Phase III), MRZ-2/579 (Phase I).
- *Antitussive* – dextromethorphan (marketed).

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