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Targeting AMPA and kainate receptors in neurological disease: therapies on the horizon?

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Aberrant excitatory neurotransmission is a prominent pathological component in many neurological and psychiatric diseases. Not surprisingly, the proteins that mediate the majority of excitatory signaling, ionotropic glutamate receptors (iGluRs), represent tempting targets for drug development efforts. This potential remains largely unrealized, however, despite a wealth of promising preclinical data. Here I discuss briefly the new applications and candidate drugs acting on the AMPA and kainate subtypes of iGluRs that suggest that a renaissance might be underway.

AMPA and kainate receptors sub-serve different roles in the brain. AMPA receptors mediate the majority of fast excitatory neurotransmission and are critical cellular constituents of learning and memory processes. Over-activation of AMPA receptors, however, can be damaging to the nervous system, producing convulsions or neuronal death. Kainate receptors play more modulatory roles, fine-tuning the balance between neuronal excitation and inhibition.

Positive AMPA receptor modulators strengthen excitatory transmission, enhance synaptic plasticity, and preclinical and preliminary clinical research suggested efficacy as cognition enhancers (Lynch, 2006; O'Neill and Dix, 2007). The first potentiator tested in large clinical trials was CX516 (Cortex Pharmaceuticals), which did not show efficacy in a variety of pathologies (eg Berry-Kravis *et al*, 2006). In contrast, a second-generation ampakine, CX717, normalized behaviors associated with attention deficit hyperactivity disorder (ADHD). Further testing of CX717 for ADHD was not approved by the US Food and Drug Administration due to toxicological concerns, although approval was granted to continue trials of CX717 in Alzheimer's disease. The outcome of this project is uncertain, however, given that a chemically distinct potentiator, LY415395 (Eli Lilly), failed to improve cognitive performance in an Alzheimer's disease trial (Chappell *et al*, 2007). Recently, compelling preclinical data prompted initiation of two Phase II trials in Germany to determine if CX717 reverses or prevents respiratory depression during opiate analgesia. These appear to be the only ongoing studies of efficacy for positive AMPA receptor modulators in humans, as clinical studies for similar molecules have been suspended (Schering-Plough) or the results remain undisclosed (Servier, GlaxoSmithKline).

Noncompetitive inhibitors of AMPA receptors, such as talampanel (Teva Pharmaceuticals) and perampanel (Eisai Medical Research), reduce over-excitation and potentially slow neuro-degeneration. These drugs were efficacious as adjunct therapies for refractory partial complex seizures (Howes and Bell, 2007); perampanel also alleviated diabetic and post-herpetic neuropathic pain and will be further tested for these indications. Results released

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from an in-progress study suggested that talampanel decreased mortality from glioblastoma, and an examination of its efficacy in amyotrophic lateral sclerosis is planned. Perampanel was not effective as an add-on therapy to levodopa in Parkinson's disease, however, and this program was terminated by Eisai.

Preclinical data suggest that kainate receptors represent an untapped and attractive target for drug development. A nonselective AMPA/kainate receptor inhibitor, tezampanel (NGX424; Torrey Pines Pharmaceutics), reduced both migraine pain and other symptoms in a recent Phase II trial. This clinical efficacy is likely attributable to inhibition of kainate receptors, based on preclinical evidence with more selective antagonists developed by Eli Lilly. A chemically distinct AMPA/kainate receptor antagonist, NS1209 (NeuroSearch A/S), also alleviated refractory status epilepticus and neuro-pathic pain in small Phase II studies, but further research into this molecule was suspended. The apparent success of the first representatives of this new class of drugs provides a strong impetus for further development and clinical testing.

It is evident from this overview that there is reason for both optimism and healthy skepticism regarding the clinical prospects of drugs targeting AMPA and kainate receptors. Cusp of a renaissance or a false dawn? Perhaps a Magic 8-Ball offers the best advice for would-be prognosticators: 'Ask again later.'

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