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The Role of AMPA Receptor Modulation in the Treatment of Neuropsychiatric Diseases

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The study of the glutamatergic neurotransmitter system has received substantial attention in recent years in the pathophysiology and treatment of neuropsychiatric disorders. Glutamate is the major mediator of excitatory synaptic transmission in the mammalian brain, and thereby contributes to important brain functions. Under normal conditions, the glutamatergic system plays a prominent role in synaptic plasticity, learning, and memory, but in pathological conditions it is known to be a potent neuronal excitotoxin, triggering either rapid or delayed neurotoxicity; it should be noted that the “toxicity” can range from atrophic changes (most likely relevant to certain psychiatric disorders) as well as overt cell death. Indeed, even modest, transient increases in the concentration of extracellular glutamate can lead to excitotoxicity and cell death (Olney 1994). Consequently tight regulation over glutamatergic neurotransmission is required to maintain optimal neuronal function to prevent overactivation of the system. Multiple levels of regulatory processes have evolved to help insure glutamatergically mediated excitation is kept within tight boundaries (Chen et al 2001). A dysfunction of the regulation of extracellular glutamate levels has been implicated in a number of neurological and psychiatric diseases including Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, Amyotrophic Lateral Sclerosis, schizophrenia, obsessive-compulsive disorder, and mood disorders (major depressive disorders and bipolar disorder). Examining the different glutamatergic components that possibly regulate glutamate in a suboptimal manner is now underway to more precisely identify the relevant targets that are contributors to disease or to diminished cognition as occurs in aging. The AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) glutamate receptor is clearly a target worth pursuing. AMPA receptors are the main contributors of excitatory neurotransmission, mediating the fast, rapidly desensitizing excitation of many synapses, and are involved in the early response to glutamate in the synaptic space. Their activation opens the pore of the channel permitting the inward flow of sodium, resulting in the depolarization of the neuronal membrane. This change in the intracellular charge releases the Mg^{2+} cation from the N-methyl-D-aspartate (NMDA) receptor channel, permitting passage of Ca^{2+} through the pore. The

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AMPA receptors are composed of a homo or heteromeric complex of four subunits (GluR1-4). Differences in subunit expression, posttranscriptional changes, and different splicing modifications provide a wide range of functional diversity and complexity to these types of receptors, through effects on desensitization time and receptor trafficking. AMPA receptors are usually co-expressed with NMDA receptors at synapses where jointly they contribute to the processes of synaptic plasticity that are involved in learning, memory, excitotoxicity, and neuroprotection (Malinow and Malenka 2002). During periods of glutamatergic excitation, AMPA receptor-mediated depolarization of the postsynaptic membrane makes it possible for activation of NMDA receptors, which initiate Ca^{2+}-dependent intracellular signaling pathways that modulate the surface presence of AMPA receptors. Modifications in AMPA receptors at the postsynaptic membrane cause changes in synaptic strength, and is a key regulator of various forms of synaptic plasticity. However, in addition to regulating “here and now” synaptic plasticity, AMPA receptors are now known to play important roles in long-term neurotrophic/neuroprotective effects. Thus, enhancing the activity of AMPA receptors has been shown to increase production of certain growth factors (e.g., Brain derived neurotrophic factor [BDNF]) (Bai et al 2003; Lauterborn et al 2000; Lauterborn et al 2003) and to regulate the mechanism of neurite growth (Voss et al 2007). This property of agents which potentiate the activity of AMPA receptors has led to widespread interest in using them to treat a variety of neuropsychiatric disorders associated with neuronal atrophy/loss.

The importance of directly modulating AMPA receptors is thus evident. However, since direct activation of AMPA receptors runs the risk of “overstimulation” and thereby the induction of epileptiform activity and/or neurotoxicity, efforts have been underway in the last decade to develop indirect AMPA receptor potentiators as a means of enhancing neuroplasticity and thus treat various neuropsychiatric disorders (Kalivas and Manji 2008). These molecules bind to allosteric sites on AMPA receptors, slow deactivation by stabilizing the clamshell in its closed-cleft, glutamate-bound conformation (Jin et al 2005) and thereby enhance signaling through the receptors. Some AMPA receptor potentiator agents have been explored in rodent models and are now entering clinical trials (Black 2005) as a means of boosting Ca^{2+} flux through the AMPA receptor, and enhancing LTP and downstream signaling pathways. The introduction of centrally active positive allosteric modulators of AMPA-type glutamate receptors led to the unexpected observation that fast excitatory transmission in behaving animals can be enhanced without causing seizures or excitotoxic damage (Staubli et al 1994b). There are in general three therapeutic areas where these types of compounds could be useful in treating central nervous system (CNS) illnesses. First, excitatory inputs regulate neurotrophin expression in the cortical telencephalon. AMPA receptor potentiators have been shown to increase production of these growth factors (e.g., Brain derived neurotrophic factor [BDNF]) (Bai et al 2003; Lauterborn et al 2000; Lauterborn et al 2003) and to regulate the mechanism of neurite growth (Voss et al 2007). This property of the AMPA receptor potentiators has led to widespread interest in using them to treat both neurodegenerative conditions and certain psychiatric disorders, most notably depression, which are hypothesized to involve deficient levels of neurotrophic factors (Mackowiak et al 2002). Second, there is data demonstrating dysfunction of glutamatergic neurotransmission in certain cognitive disorders. AMPA receptor potentiators in this framework would serve to rectify these cognitive deficits (Lynch 2002). Finally, increasing excitatory neurotransmission is a way for promoting the induction of long-term potentiation (LTP) (Staubli et al 1994a), a form of synaptic plasticity widely regarded as a substrate of memory. Early work recognized that AMPA receptor potentiators make possible the formation of LTP and thus are logical candidates for memory-enhancing drugs which might be particularly useful during aging.

It is this latter area of AMPA therapeutic development that Bloss et al. (Bloss et al 2007) have made an important contribution to our understanding the behavioral and biological effects of chronic treatment with a positive AMPA receptor modulator during aging.

In their experiment, they administered either two doses of the AMPA potentiator S18986 (0.1 and 1.0 mg/kg) or a control for 4 months in both a young (approximately 2.5 months) and an older cohort (approximately 19 months) of rodents. These two groups were compared at the end of the treatment phase on a series of tests including the Y-maze performance to investigate changes in locomotor activity and as a measure of hippocampal dependent memory, the tyrosine hydroxylase immunoreactivity in substantia nigra pars compacta and anti-choline acetyltransferase immunoreactivity in the medial septum and the diagonal band of Broca, and BDNF mRNA in *in situ* hybridization. The investigators found that chronic administration of the AMPA potentiator S18986 in rats increases locomotor activity and performance in a spatial memory task. In addition, chronic treatment with the AMPA potentiator significantly reduced decreases in tyrosine hydroxylase and choline acetyltransferase immunoreactivity in regions studied in the older cohort of rodents. The density of hippocampal OX-42, a known marker for brain microglia which increases with age, also significantly decreased with chronic exposure to S18986. The investigators postulated that chronic administration of S18986 may be acting through neurotrophin increase, particularly an increase in BDNF expression.

This elegant and comprehensive study shows that chronic AMPA modulator treatment protects tyrosine hydroxylase and choline acetyltransferase producing cells in critical regions that have been reported to be particularly susceptible to neurodegeneration effects during aging. Such results invite considerable enthusiasm as they expand the current knowledge base on AMPA receptor potentiators as a promising group of compounds that could possibly either attenuate or reverse the cognitive decline seen in normal aging and in certain neurological and psychiatric conditions. The results of this study provide the framework for future studies that examine the potential utility of AMPA modulators on brain aging and cognition.

Not only are there normal physiological changes associated with aging such as decreased memory but individuals at a later age are vulnerable to a whole host of neurodegenerative diseases as well. Namely they include Parkinson's disease, Alzheimer's disease, and other neurodegenerative diseases. Thus, reducing, preventing, or, reversing damage to key cells involved in these illnesses would be a major public benefit. Many of these neuropsychiatric diseases occur in later life and as our society ages; age-related diseases will likely increase in prominence as both individual and public health concerns. Disorders of cognition are particularly important and Alzheimer's disease is by far the most common cause of dementia of the elderly. In 2000, the prevalence of Alzheimer's disease in the United States was estimated to be approximately 4.5 million individuals, and this number has been projected to increase to 14 million by 2050 (Brookmeyer et al 1998). These numbers illustrate to the seriousness of its impact. Milder degrees of cognitive dysfunction may precede the clinical diagnosis of probable Alzheimer's disease, such as mild cognitive impairment (Kelley and Petersen 2007).

While the potential benefit of AMPA receptor modulators in classical neurodegenerative disorders should be apparent, it is noteworthy that emerging data also suggests that they may have considerable utility in the treatment of severe psychiatric disorders. Indeed, it is now clear that all complex behavioral phenomena—including mood and emotion—are dynamic processes that rely on plastic neural circuitry. Research on the biological underpinnings of psychiatric disorders has therefore moved away from focusing on absolute changes in neurochemicals such as monoamines and neuropeptides, and instead has begun highlighting the role of neural circuits and synapses, and the plastic processes controlling their function. Thus, these illnesses can best be conceptualized as genetically influenced disorders of synapses and circuits rather than simply as deficits or excesses in individual neurotransmitters. For example, bipolar disorder a major medical illness characterized by recurrent episodes of disturbed mood, cognition, motoric behavior, hedonic tone, as well as changes in psychovegetative function, and systemic health manifestations (e.g., diabetes, cardiac disease) is now hypothesized to arise from abnormalities in synaptic and neuronal plasticity cascades,

leading to aberrant information processing in critical synapses and circuits (Schloesser et al 2008). Supporting the importance of synaptic plasticity in mood disorders is that several drugs that are useful in the treatment of mood disorders (e.g., lamotrigine, riluzole, and valproate) have been shown to target intracellular signaling pathways that control synaptic plasticity and cellular resilience; whether this is important to their therapeutic effects in mood disorders is unknown at this time. For example, it was recently found that the anticonvulsants lamotrigine, riluzole, and valproate regulate GluR1/2 subunit AMPA receptor surface levels and function and such effects may be responsible for their different clinical profile (antimanic or antidepressant) (Du et al 2007).

Supporting evidence for the potential beneficial role of AMPA receptor modulators in the treatment of mood disorders includes studies showing that the biarylpropylsulfonamide AMPA receptor potentiators (LY392098 and LY451616) have antidepressant effects in a variety of animal models of depression (including the application of inescapable stressors, in learned-helplessness models of depression, and in animals exposed to chronic mild stress procedure) (Li et al 2001). In contrast to traditional antidepressants, this group of compounds does not appear to affect the extracellular concentration of monoamines (Skolnick et al 2001). However, they can enhance the neurotrophic actions of BDNF mRNA and protein in primary neuronal cultures (Lauterborn et al 2000; Lauterborn et al 2003). Modulation of neurotrophic factor expression and modifying the degree of neurogenesis may be decisive factors in understanding the therapeutic effects of antidepressants and mood stabilizers in mood disorders and more importantly in the mechanism of antidepressant action of AMPA receptor modulators. A twist to this hypothesis is that recent evidence suggests that full antidepressants may happen within a few hours with the AMPA throughput enhancer ketamine in a timeframe when neurogenesis would not be expected to occur. All traditional monoaminergic antidepressants have a considerable lag of weeks to months for full antidepressant response. Enhancing synaptic potentiation by increasing AMPA throughput may be important in the initial onset of antidepressant effects. Such a theory has recently been proposed as a strategy for developing antidepressants that have a rapid onset of action (Maeng et al 2007).

Future Directions

In future studies, the neuroprotective, cognitive enhancing, neuroplastic, and synaptic plasticity enhancing effects of AMPA potentiators should be further delineated first in preclinical then in clinical studies. Indeed, a number of AMPA potentiators are now being explored in CNS diseases including Parkinson's disease, major depression, alcohol intoxication, and cognitive deficits in Alzheimer's disease (Bleakman et al 2007; Jones et al 2007; O'Neill and Witkin 2007) as well as for the use as cognitive enhancers (O'Neill and Dix 2007). Some early studies indicate mixed results. The AMPA receptor potentiator Farampator (500 mg) improved short-term memory but appeared to impair episodic memory in healthy elderly volunteers (Wezenberg et al 2007). In another study, the CX516 showed no improvement in cognitive deficits or psychotic symptoms in patients with schizophrenia (Goff et al 2007). The AMPA potentiator LY451395 also failed to show cognitive improvement in patients with Alzheimer's disease (Chappell et al 2007); however, it is noteworthy that this study did show improvements in neuropsychiatric symptoms. It is perhaps too early to speculate on the reasons for these failed clinical trials, but as described above there is a wide range of functional diversity and complexity to the AMPA receptors and naturally all AMPA receptor modulators will not behave the same. Certainly, a better understanding of the molecular cellular mechanisms involved in disease and the mechanism of action of AMPA receptor modulators will be of the utmost importance when embarking in proof-of-concept studies.

Finally, the results of Bloss et al. raise an intriguing question: namely, precisely what role will AMPA potentiators have with respect to the treatment of cognitive disorders? Will their role

be to prevent, attenuate, or reverse cognitive decline? The answer to each will require different types of studies to more precisely delineate the role of AMPA potentiators in aging and neuropsychiatric diseases. Thanks to the study by Bloss and colleagues we are coming to a better understanding on the extent of the neuroprotective and cognitive enhancing effects of one of the AMPA potentiators. Such results should help pave the way for future studies carried out with other AMPA receptor modulators.

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