

Glutamate: leader in contemporary translational neuropsychopharmacology research

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In humans, neocortex represents about 85% of the total brain mass. Modern stereological methods have estimated that about 80% of neurons in neocortex are spiny and excitatory and form 85% of all synapses, while about 20% of the neurons are smooth and inhibitory, forming 15% of the synapses (1). Glutamate is the main excitatory neurotransmitter in the central nervous system and exerts its effects through the activation of several receptor subtypes. It mediates fast excitatory synaptic transmission between neurons through the Ionotropic receptors amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA), N-methyl-d-aspartate (NMDA), Kainate and Metabotropic receptors. It has been suggested that dysregulation of the glutamatergic system is implicated in a variety of psychiatric disorders such as schizophrenia, major depression, aggression and substance use disorders.

Major Depression

A large majority of studies have provided evidence of reduced glutamate metabolite levels in the frontal cortex and cingulate regions of patients with major depressive disorder in the midst of a current depressive episode (2,3). First it was shown, by using microdialysis *in vivo*, that a single administration of the atypical antidepressant tianeptine, 30 minutes prior to acute restraint stress, completely abolished the increase of extracellular glutamate levels induced in basolateral amygdala by acute restraint stress (4). In line with this rationale, ketamine, a nonselective NMDA-R antagonist mainly employed as a dissociative anesthetic, has been shown at subanesthetic doses to induce rapid (within 24 h) antidepressant effects that are sustained for at least several days after a single infusion, in at least four blinded pilot clinical trials (5). Traditional limitation of strategies based on compounds targeting ionotropic glutamate receptors has been the presence of considerable side effects. An alternative has been offered by compounds affecting metabotropic glutamate receptors, which are crucial for the regulation of glutamatergic neurotransmission as well as for other neurotransmitters involved in mood disorders.

Aggression

Of the various glutamate receptors, NMDA receptors appear to be the most promising targets for pharmacological intervention in treating aggression. Glutamate activity has been localized to various brain regions in rat, including the hypothalamus, lateral septum, bed nucleus of the stria terminalis, and medial amygdala (6), areas of the brain implicated in aggressive behavior (7). For instance, in rats, the "hypothalamic attack area" has been shown to possess dense glutamatergic activity (8), and infusion of L-glutamate itself into a similar region of the cat hypothalamus activates an aggressive response (9). Clozapine differentially modulates and enhances frontal NMDA receptor density in chronically treated rodents reared in isolation (10). Also lamotrigine's antiaggressive effects may manifest due to blockade of voltage-gated Na⁺ channels (11) and A-type K⁺ channels as well as by inhibiting excitatory postsynaptic currents via voltage-gated sodium and calcium channel blockade (12) resulting in inhibiting overexcited neuronal activities without significantly altering basal rates. Pavlovic has shown that augmentation of clozapine with lamotrigine in patient with chronic schizophrenia synergistically decreased aggression (13).

Cocaine Dependence

Glutamate neurotransmission also plays a significant role in drug reward and reinforcement and glutamate receptors may be therapeutic targets for the treatment of cocaine dependence (14). Recent preclinical studies reveal that glutamate projections from the prefrontal cortex to the nucleus accumbens are critical for cue-, stress- and cocaine-primed reinstatement of previously extinguished cocaine self-administration in animals (15). The glutamate ionotropic receptor agonist AMPA infused into the nucleus accumbens reinstates cocaine self-administration, whereas blocking translation and expression of the AMPA receptor subunit (by antisense oligonucleotides) attenuates this behavioral effect. Glutamate levels were also positively correlated with years of cocaine use suggesting that the changes in glutamate developed as a result of exposure to cocaine (16). Neuroplastic changes occur in response to exposure to drugs of abuse, the persistence of these changes beyond termination of drug administration suggest these chronic changes may be involved in dependent users increased susceptibility to relapse to drug taking even after a period of abstinence (17). Cocaine can induce Long Term Potentiation in the ventral tegmental area of excitatory afferents onto dopaminergic cells (18), which is mediated by AMPA and NMDA glutamatergic receptors (19). Taken together, pharmacotherapies that mediate glutamate neurotransmission in particular could theoretically reverse aberrant cocaine-induced neuroplastic changes and prevent future relapse in humans (20,21). Reversing long-lasting neuroplastic changes linked to glutamate dysregulation and relapse may provide greater benefit rather than targeting dopaminergic neurotransmission directly. Pavlovic has shown that biomodal action of lamotrigine due to its glutamatergic properties, significantly reduced craving by decreasing depressive symptoms and prevented relapses in patient with cocaine dependence (22).

Alcohol Dependence

Mesolimbic dopamine reward circuitry is composed primarily of dopamine-synthesizing neurons in the ventral tegmental area of the ventral midbrain that project rostrally to target regions such as the nucleus accumbens, amygdaloid complex and frontal cortex. Each of these regions receive substantial glutamatergic input (23,24). In response to chronic inhibition of NMDA receptor function, repeated ethanol exposure induces an upregulation of various NMDA receptor subunits including in the cerebral cortex and hippocampus, ventral tegmental area and amygdala (25,26), regions that are critical for the reinforcing effects of ethanol. In addition to up-regulating NMDA subunit expression, chronic ethanol also increases NMDA receptor functionality (i.e. conductance, cat-

ion influx, etc.) (27) and synaptic clustering of the receptor (28). In animals and humans, this CNS hyperexcitability manifests itself as a propensity towards seizure-like activity, which can be suppressed by NMDA antagonists (29). Pavlovic has shown that this hyperexcitability in withdrawal phase could be attenuated by lamotrigine due to its effect on glutamate and that reduction of craving and withdrawal symptoms lead to relapse prevention (30).

Currently numerous molecules affecting glutamatergic neurotransmission are in preclinical and clinical phase and are aiming to address most difficult to treat symptoms non-responsive to currently available drugs. Most advanced are testing on effectiveness of glycine transport inhibitors for negative symptoms in schizophrenia and metabotropic glutamate 2/3 antagonist for cognitive symptoms in depression. If successful the door of glutamate-specific therapies will finally be open.

Conflict of Interest

The author is employed at PRA International, Mannheim, Germany. The article reflect personal opinion of the author exclusively.

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