

Differential effect of β -N-oxalylamino-L-alanine, the *Lathyrus sativus* neurotoxin, and (2)- α -amino-3-hydroxy-5-methylisoxazole-4-propionate on the excitatory amino acid and taurine levels in the brain of freely moving rats.

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Summary

A study was conducted on the effect of β -oxalylamino-L-alanine (BOAA or ODAP), a glutamate analog present in *Lathyrus sativus* seeds and implicated in the etiopathogenesis of neurolathyrism, and (2)- α -amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) on the extracellular levels of aspartate, glutamate and taurine in the primary motor cortex of freely moving rats. It was found that while both neurotoxins increased the level of aspartate and glutamate, only AMPA was able to modulate the level of taurine. GYKI-52466, a non-competitive non-NMDA antagonist, inhibited BOAA-induced increase of aspartate, but not that of glutamate. Conversely, this antagonist proved to be very efficient in blocking the stimulating effect of AMPA on all three amino acids.

It is suggested that BOAA increases the level of glutamate *in vivo* by a mechanism not connected to its effect on the non-NMDA receptors, which might involve the inhibition of glutamate transport. This would allow the excitatory neurotransmitter to reach a concentration sufficient to stimulate the non-NMDA receptors, which in their turn mediate the specific release of aspartate. Although the role of aspartate as a neurotransmitter is still under discussion, it might indeed amplify the excitotoxic cascade through its action on NMDA receptors. It is speculated that this sequence of events might represent an important step in the molecular cascade leading to the appearance of the selective motoneuron degeneration in neurolathyrism.

Following commentary by Peter Spencer, Oregon Health Sciences University, Portland, Oregon, USA (Email: spencer@ohsu.edu)

Vincenzo LaBella and Federico Piccoli propose in their recent paper ⁽¹⁾ that BOAA (i.e. ODAP) increases the level of the excitant neurotransmitter glutamate *in vivo* by a mechanism that is not connected to its action on the AMPA subclass of glutamate receptors on nerve cell plasma membranes in the central nervous system (CNS). The latter is the molecular mechanism by which the grass pea neurotoxin is widely believed to exert its excitotoxic action on nerve cells; this culminates in the cortical motor nerve cell degeneration that underlies the spastic paraparesis of lathyrism. Instead, LaBella and Piccoli propose that BOAA acts primarily by inhibiting the uptake of glutamate, thereby allowing the activation of glutamate receptors which in turn mediate the specific release of aspartate, a second putative excitatory neurotransmitter which could amplify an excitotoxic cascade via another subclass (NMDA) of glutamate receptor. Ross and colleagues ⁽²⁾ earlier provided *in vitro* evidence that BOAA (1 mM) markedly inhibits both the transport (reuptake) of glutamate and aspartate but not the transport of inhibitory neurotransmitters GABA or glycine. However, the concentration of BOAA that induced this effect was orders of magnitude greater than that required to displace AMPA binding to cortical membranes *in vitro* and the induction of neuronal degeneration in mouse cortical slices in culture ^(2,3). Relatively high concentrations of BOAA (100-250 micromolar) and lower concentrations of AMPA (1-100 micromolar) were required to induce elevated concentrations of aspartate and glutamate in the motor cortex of the freely moving rat elegantly studied by LaBella and Piccoli ⁽¹⁾. The administration of AMPA antagonists blocked the AMPA effect but not the BOAA effect, thereby suggesting that at these concentrations BOAA may be acting to increase the concentration of excitatory amino acids by a route other than via the AMPA receptor.

These new observations continue efforts from a number of laboratories to define the molecular mechanism of the grass pea neurotoxin. A satisfactory explanation will account for the stereospecific CNS neuronotoxic action of L-BOAA acting at physiologically relevant concentrations (not well defined) in the motor cortex. To date, L-BOAA but not D-BOAA, has been shown to induce neuronal degeneration in tissue culture ⁽²⁾ via a mechanism that is consistent with the stereospecific action of L-BOAA at the AMPA receptor ⁽³⁾. It will be important, therefore, to determine whether the newly proposed mechanism of BOAA neurotoxicity *in vivo* displays

molecular stereospecificity at physiological concentrations likely to be encountered in humans ingesting grass pea.

Acronyms

AMPA - α -amino-3-hydroxy-5-methylisoxazole-4-propionate

BOAA - β -N-oxalylamino-L-alanine; synonym for β -N-oxalyl-L- α , β -diaminopropionic acid (ODAP)

CNS - central nervous system

GABA - γ -amino-butyric acid

NMDA - N-methyl-D-aspartic acid

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