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Letter to the Editor

Excitatory Amino Acids Interaction and Neurotoxicity

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Letter to the Editor

The rationale for this letter is Olney's conclusion [1,2], the precursor of research focused on the excitotoxic action of excitatory amino acids, as well as Kostic et al [3] that damage over 80% of neurons results in the typical symptoms of Parkinson's, and multiple sclerosis disease. The substance responsible of this neurons degeneration is Glutamic acid [Glu]. This acid is one of the strongest (except aspartic acid) excitatory neurotransmitters. It occurs in all structures of the CNS and ANS as well as in tissues organs where it stimulates specific receptors. The construction of Glu receptor is very complicated, because it consist an ion- (NMDA) and metabotropic (mGlu) part, as well as various other binding sites, including polyamines or glycine.

There exists also a second biological GluR stimulant (aspartic acid, N-methyl-D-Aspartic Acid =NMDA), which in deficit or lack of Glu replaces it in the stimulation of the same neural tissue structures. It remains unknown, to what extent Glu acid and Asp acid are complementary, and to what extent they have an additive or super additive effect in disturbed homeostasis, due to lack e.g. ATP or other substances significantly important in the processes of neuronal transduction. Especially since applied on a large scale in pregnant for anesthesia/analgesia ketamine (nonselective inhibiting of iNMDARs), may cause neurodegenerative changes in the foetus. That is interesting to clarified, if the NMDAR is inhibited that endogenous Glu may act by uninhibited mGluR or this is the result of uncontrolled intracellular and/or mitochondrial receptors activation or perhaps damage to the cell structures (e.g. cell membrane). It is interesting investigate the molecular mechanisms of ketamine neurotoxic action on progenitor cells and definitive neurons of brain structures (hypothalamus, hippocampus and prefrontal cortex, certainly). Neurodegenerative action of ketamine will be verified with known Glu-derived excitotoxicity and to examination of different substances (DA, GABA, OXY) that may have a shielding effect on neurotoxic action of analyzed molecules. In particular, that some protection properties against glutamate neurotoxicity have been already demonstrated for dopamine [4]. There are also reports of existing interactions between Glu and GABA as well as Glu an OXY, both in humans and animals [5].

Interaction of Glutamate and Oxytocin (OXY)

It is supposed that Glu, and OXY are synthesized and stored in the same structure and parts of the brain. Both Glu and its receptors are located in different neurosecretory nuclei of the hypothalamus which are associated with neuroendocrine function. It have been demonstrated the presence of Glu in *nucleus Paraventricularis* (PVN), *nucleus Ventro-Medianus* (VMN), *nucleus arcuatus, nucleus Supraopticus* (SON), *eminentia mediana* and *infundibulum* of hypophysis [6]. In the pituitary gland Glu was found in pituicytes and terminal axons of hypothalamic neurosecretory cells reaching to the posterior pituitary [7]. Moreover mGluRs have been detected in different regions of hypothalamus and pituitary three parts [8], and expression of the gene GLU - mainly in the vicinity of hypothalamic related with the regulation of neuroendocrine activities. Distribution of mGluR in area relevant to process of reproduction and neuroendocrine activities may be the main role of Glu in the regulation of these phenomena (OXY is synthesized primarily in giant nuclei neurons of the PVN and SON of hypothalamus) [9]. Additional evidence of the interaction between Glu and OXY derived from animal studies. Pampillo et al [10] have shown that in adult male rats Glu regulates the release of hypothalamic OXY by mGluR stimulation and excitation of cAMP signal transduction. Similarly Morsetta et al [11] demonstrated that mGluR stimulation increases the *in vitro* release of OXY from rat hypothalamic-pituitary tissue sections. Studies conducted on animals treated with phencyclidine - specific antagonist of ion channels of NMDARs exhibit inhibition of prepulse. This is similar to the neurological situation in which a weak impulse inhibits the body's reaction to a stimulus, respectively stronger, what was found in adult schizophrenics. Data concerning schizophrenia and other psychiatric disorders, may also suggest a link between Glu and OXY [12]. Long-term use of phencyclidine in male rats resulted in shortening the time to establish social and societal relationships [13]. There is still unknown mechanism which would explain the changes in social behavior caused by the drug, but it seems that the principal mediator of such behavior in rodents is the endogenous OXY. Studies performed by Caldwell et al [14] appear to confirm this hypothesis. In model of OXY knockout mice phencyclidine treatment increases prepulse inhibition in comparison to wild-type mice, what suggest that OXY is a natural antipsychotic compound. In addition Le et al [15] demonstrated that long-term use of phencyclidine in rats inhibits transcription of oxytocin mRNA in PVN of the hypothalamus and significantly reduce the OXY uptake by receptors. Moreover, OXY therapy returns social behavior inhibited by chronic use of phencyclidine.

This is interesting to verify unresolved research hypothesis of cellular damaging mechanism of ketamine (nonspecific iNMDAR's antagonist) in comparison to Glu action (neuroexcitotoxicity). The neurotoxicity model enable to recognized molecular mechanism of Glu and ketamine action, what is especially important in the treatment of neurodegenerative civilization diseases.

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Glutamate is widely used as a food flavor enhancer. It may gradually move to the CNS, and may cause time-dependent damage fetus neurons and/or developing after birth, which in turns may resulted in neurodegeneration of the CNS structures responsible for motility and/or emotions organisms known form of degenerative diseases in humans and animals. Paradoxically NMDA inhibitors such as memantine or phencyclidine are designed to prevent or protect the structure of the brain from glutamate neurotoxicity.

The Neurotoxicity of Glutamate

Contrary to the assertions of universal role of Glu as the main stimulating neurotransmitter, in excess it is unfortunately highly toxic to neurons. This negative influence of Glu is called neuroexcitotoxicity [16]. Even at low concentrations Glu supplementation to neuronal cultures, irreversibly destroyed them. Already in 1970 have been demonstrated that orally administered Glu causes degenerative changes in neurons. These conclusions caused a general alarm, because the Na-Glu is widely used as a food supplement. Is a well-known Chinese restaurant syndrome, consisting of a sharp attack neck stiffness and pain in the chest, after a meal seasoned with this compound, but the possibility of neurotoxic action of Glu in this disease is rather hypothetical. To induce postneurotoxic failures (for experimental purposes) local injection of kainic acid is used. It stimulate local neurons to release of Glu (selectively stimulating both NMDA and mGlu receptors) which resulted in the death of neurons [17]. The primary factor in the development of Glu excitotoxicity is an excess of release Ca^{2+} ions. The mechanisms leading to this condition and to facilitate cell death they are:

*Glutamic acid stimulates NMDAR, AMPAR and mGluR. Activation of AMPA receptors depolarizes the cell, which unblocks NMDA channels [18], which allows to influx of free Ca^{2+} to the neuron. Depolarization of neuron fiber terminations opens Voltage-Calcium Channels (VGCC), which intensify Glu release. Stimulation of mGluR Glu in turns causes the release of intracellular Ca^{2+} from endoplasmic reticulum. As a result of those changes Na^{+} passes into the cell and facilitating the entry of Ca^{2+} by stimulating the exchange of Ca^{2+}/Na^{+}. Depolarization inhibits the reuptake of Glu, and ultimately increasing extracellular concentrations of Glu.

*In homeostasis exists a mechanisms counteract increased $[Ca^{2+}]_i$ concentration, which operate by pumping Ca^{2+} outside the cell and indirectly by pumping Na^{+} ions.

•The mitochondria and endoplasmic reticulum act as capacious sinks for Ca^{2+} and normally keep $[Ca^{2+}]_i$ under control. Loading of the mitochondrial stores beyond a certain point, however, disrupts mitochondrial function, reducing ATP synthesis, thus reducing the energy available for the membrane pumps and for Ca^{2+} accumulation by the endoplasmic reticulum. Formation of Reactive Oxygen Species (ROS) is also enhanced. This represents the danger point at which positive feedback exaggerates the process.

•Raised $[Ca^{2+}]_i$ affects many processes, the chief ones relevant to neurotoxicity being:
- increased Glu release

- Activation of proteases (calpains) and lipases, causing membrane damage.

- Activation of Nitric Oxide Synthase (NOS); while low concentrations of nitric oxide are neuroprotective, high concentrations in the presence of ROS generate peroxynitrite and hydroxyl free radicals, which damage many important biomolecules, including membrane lipids, proteins and DNA.

- Increased Arachidonic acid release, which increases free radical production and also inhibits Glu uptake.

Glutamate and Ca^{2+} are arguably the two most ubiquitous chemical signals, extracellular and intracellular, respectively, underlying brain function, so it is disconcerting that such cytotoxic mayhem can be unleashed when they get out of control. Both are stored in dangerous amounts in sub cellular organelles, like hand grenades in an ammunition store. Defense against excitotoxicity is clearly essential if our brains are to have any chance of staying alive. Mitochondrial energy metabolism provides one line of defense, and impaired mitochondrial function, by rendering neurons vulnerable to excitotoxic damage, may be a factor in various neurodegenerative conditions, including Parkinson disease [above cit. accordingly to Rang et al. [19]].

The role of excitotoxicity in ischaemic brain damage is well established, and it is also believed to be a factor in other neurodegenerative diseases, such as those early was discussed [20].

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