

EFFECT OF EXCITATORY AMINO ACIDS ON ACTIVITY OF VASOPRESSINERGIC AND OXYTOCINERGIC NEURONS

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A few compounds function as the excitatory amino acid (EAA) transmitters in the central nervous system (CNS), but glutamate (Glu) is the most important. Data on Glu participation in the control of vasopressinergic (AVP-ergic) and oxytocinergic (OXT-ergic) neuronal activity have been collected mainly on the basis of observations of hypothalamic AVP-ergic and OXT-ergic neurons. *In vivo* and *in vitro* experiments have demonstrated that Glu enhances bioelectric activity of the aforementioned neurons and increases AVP and OXT release. However, inhibitory effect of Glu on AVP-ergic neurons, mediated by local GABA-ergic interneurons, is also possible. Both ionotropic and metabotropic receptors participate in EAA effect on AVP-ergic and OXT-ergic neurons. EAA involvement in AVP and OXT release after osmotic stimuli and in OXT release during the milk ejection reflex has been demonstrated. Recent findings demonstrated that EAA enhanced AVP release into the extracellular fluid of hippocampus in the rabbit.

Key words: Vasopressinergic and oxytocinergic neurons – Excitatory amino acids – Hypothalamus – Hippocampus – Glutamate

The interest in the role of excitatory amino acids (EAA) in cerebral functions increased rapidly in the 1990's. They are considered to be the most important excitatory neurotransmitters in the central nervous system (CNS). They are involved in neuroendocrine regulation, in learning and memory-related processes, as well as in pathophysiology of many diseases (BRANN 1995).

Amino acids functioning as excitatory neurotransmitters. The most important transmitters in the group of excitatory amino acids are glutamate (Glu) and aspartate (Asp). Other amino acids, such as L-homocysteic acid (L-HCA), quinolinic acid – a metabolite of tryptophan and a dipeptide, N-acetyl-L-aspartyl-L-glutamic acid (NAAG), may also act as EAA in CNS, see Fig. 1 (BRANN 1995). Among all the aforementioned EAA, glutamate, found to occur in the largest quantities, plays the most important role in the CNS (FONNUM 1984). Excitatory amino acids are released from presynaptic terminals as a result of cell membrane depolarization, in a Ca^{2+} -dependent manner.

Excitatory amino acid receptors. The released EAA bind to specific receptors in the postsynaptic membrane causing its excitation. Glutamate receptors have been classified as ionotropic and metabotropic. The ionotropic ones are coupled with specific ion channels, the function of which they regulate, whereas the metabotropic ones influence, via proteins G, the synthesis of secondary cellular transmitters and subsequently the cellular metabolism. Ionotropic receptors include: NMDA (N-methyl-D-aspartate receptors), and non-NMDA, i.e. kainate and AMPA (DL- α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) (BRANN 1995). Metabotropic receptors include 8 receptor subtypes distinguished by different pharmacological profiles (mGluR_{1-8}) (RIEDEL and REYMANN 1996).

Distribution of vasopressinergic and oxytocinergic neurons in the brain. The main location of vasopressinergic (AVP-ergic) and oxytocinergic (OXT-ergic) neurons in mammals are magnocellular hypothalamic nuclei, the supraoptic nucleus (SON) and the

paraventricular nucleus (PVN). The nerve fibers from that area project predominantly towards the posterior pituitary lobe and the median eminence (VAN LEEUWEN et al. 1979). Moreover, the hypothalamus contains magnocellular AVP-ergic and OXT-ergic neurons forming the so-called accessory hypothalamic nuclei with different locations, projections and sensitivity to stimuli in different animal species (SOFRONIEW 1983).

Parvocellular AVP-ergic neurons are concentrated mainly in the suprachiasmatic nucleus (SCN) of the hypothalamus, from which they project towards the organum vasculosum of the lamina terminalis (OVLT), the lateral septum and the lateral habenula nucleus (SOFRONIEW and WEINDL 1978). Parvocellular neurons located in the posterior portion of the PVN, synthesizing predominantly AVP, but also OXT, project with their axons to distant extrahypothalamic regions, e.g. to the limbic system, medulla oblongata and spinal cord (BUIJS 1978). Large groups of parvocellular AVP-ergic neurons have been identified within the bed nucleus of the stria terminalis (BNST) and in the medial amygdala (SOFRONIEW 1985). Populations of parvocellular neurons have been also localized in the locus coeruleus (LC), in the vertical limb of the nucleus of the diagonal band and in the medial and lateral septum (SOFRONIEW 1985).

Besides AVP-ergic neurons, OXT-ergic ones have also been found in the BNST (SOFRONIEW 1985; INGRAM and MOSS 1992), as well as in the amygdala, hippocampus, septum and locus coeruleus (SOFRONIEW 1983).

Significant species-related differences in the distribution of AVP-ergic and OXT-ergic neurons in different animals should be emphasized. For instance, AVP-ergic fibers abundantly present in the lateral septal nucleus of the rat do not occur in that structure in the rabbit (BUIJS, unpublished observations, according to WANG et al. 1997).

Recently, the presence of AVP-ergic neurons has been observed within the pyramidal cell layer of CA1-3 hippocampal areas and the dentate gyrus in rat (HALLBECK et al. 1999). The authors suggest the presence of vasopressinergic cell bodies in these structures (HALLBECK et al. 1999). Neurons located in the amygdala have been regarded to date as the only source of vasopressin in the hippocampus (CAFFE et al. 1987). However, no vasopressinergic neurons have been identified in the amygdala of primates, where only oxytocinergic neurons are present (WANG et al. 1997).

Effect of excitatory amino acids on hypothalamic AVP- and OXT-ergic neurons and AVP and OXT release. The observations of the effect of EAA on AVP-

ergic and OXT-ergic neurons made so far concern mainly the neurons located in the hypothalamus. Both within the SON and the PVN the presynaptic buttons demonstrated considerable glutamate immunoreactivity, accompanied by a lower level of aspartate immunoreactivity (VAN DEN POL 1991). Localization of glutamatergic/aspartatergic neurons projecting to the supraoptic nucleus in the rat has been recently demonstrated (CSAKI et al. 2002). Determination of the numbers of particular types of nerve terminals localized on AVP- and OXT-ergic neurons in the SON demonstrated the glutamate (Glu-ergic) terminals to account for 1/3 of the total innervation of that nucleus (MEEKER et al. 1993). Quantitatively, the innervation of AVP- and OXT-ergic neurons by Glu-ergic terminals in that nucleus is similar (EL MAJDOUBI et al. 1996). It changes considerably in the periods of secretory activation of these neurons, e.g. the number of Glu-ergic terminals on OXT-ergic neurons in rat SON increases during lactation (THEODOSIS et al. 1995). All types of glutamate receptors have been found in rat hypothalamus, with relative predominance of NMDA (MEEKER et al. 1993). On the other hand, a comparison of the distribution of Glu receptors in both magnocellular hypothalamic nuclei demonstrates higher density of these receptors in PVN than in SON (MEEKER et al. 1994). Excitatory amino acids are known to increase intracellular Ca^{+2} levels in the cells exposed to their effect (VAN DEN POL et al. 1990). Different pathways of this process after excitation of ionotropic and metabotropic receptors in SON neurons have been demonstrated. Activation of ionotropic NMDA and non-NMDA receptors results in an inflow of Ca^{+2} from the extracellular space into the neurons, whereas activation of metabotropic receptors causes a release of Ca^{+2} from the intracellular stores of these neurons (HATTORI et al. 1998). OXT-ergic neurons receive Glu-ergic transmissions primarily via AMPA, and AVP-ergic neurons via NMDA receptors (ARMSTRONG and STERN 1998). Both the number of Glu-ergic terminals located on magnocellular SON neurons and the number of Glu receptors, as well as the role of various subunits in their activity are flexible and variable depending on the type of physiologic stimuli (PAK and CURRAS-COLLAZO 2002).

The effect of EAA on the activity of AVP- and OXT-ergic hypothalamic neurons and the role of Glu receptors involved in the process was investigated. It was demonstrated in *in vitro* experiments on superfused explants of rat hypothalamus that EAA induce cell membrane depolarization of magnocellular SON neurons (HU and BOURQUE 1991). Moreover, Glu receptor antagonists di-

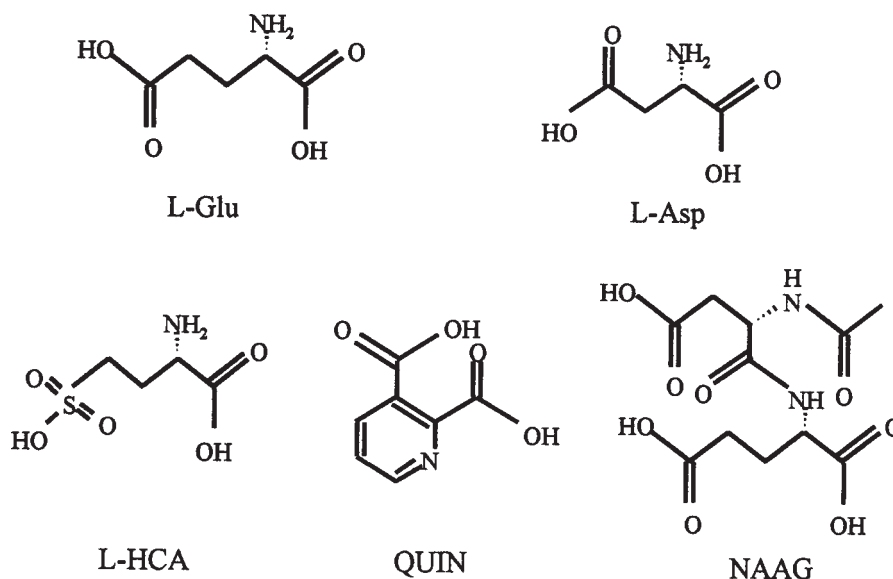


Fig.1 Formulas of endogenous excitatory amino acid neurotransmitters present and acting in the brain

minished or eliminated evoked depolarizing postsynaptic potentials and reduced the amplitude and frequency of spontaneous postsynaptic potentials recorded from magnocellular neurons in the SON. This allowed to state that these receptors are involved in the mechanism of both types of bioelectric activity of these neurons (GRIBKOFF and DUDEK 1990). The result of such effect of EAA on magnocellular SON neurons is the release of AVP into the fluid incubating explants of the hypothalamoneurohypophyseal system in *in vitro* experiments (COSTA et al. 1992; SLADEK et al. 1995). Excitatory amino acids may also exert an inhibitory effect on the release of AVP from the hypothalamic slices into the incubating fluid, which is explained by their indirect influence on AVP-ergic neurons mediated by local GABA-ergic neurons releasing an inhibitory transmitter, γ -aminobutyric acid (JOANNY et al. 2000). The bioelectric activity of OXT-ergic neurons (RICHARDSON and WAKERLEY 1997; JOURDAIN et al. 1998) and OXT release (PAMPILLO et al. 2001) are also stimulated by EAA. However, the bioelectric response of AVP- and OXT-ergic neurons to EAA may differ for both cell types, which is dependent on the type of receptors mediating the effects of these transmitters (STERN et al. 1999). The patterns of activity observed for AVP- and OXT-ergic neurons after the activation of AMPA receptors are completely different, whereas NMDA receptor-mediated excitation patterns are very similar for both types of neurons (STERN et

al. 1999). The Glu-ergic neurons identified within the PVN are equipped with α_1 -adrenergic receptors. Thus, it can be concluded that EAA released from local glutaminergic interneuron terminals in the PVN may mediate the well-known excitatory effect of norepinephrine on magnocellular neurons of that nucleus and on the release of AVP and OXT (DAFTARY et al. 1998). The effect of EAA on bioelectric activity of AVP- and OXT-ergic neurons (MOSS et al. 1997) and the release of both neuropeptides (BISSET and FAIRHALL 1996) has been confirmed by *in vivo* experiments. However, OXT-ergic neurons should be considered to respond to EAA more actively than AVP-ergic ones, because intravenous injections of NMDA caused more significant OXT release than that of AVP in rats (JEZOVA and MICHAJLOVSKIJ 1992). Increased AVP release into the femoral vein blood and blood flowing from the sella turcica region was observed after NMDA injection into the internal carotid artery in rats (GORACA 1998).

Excitatory amino acids are involved in signal transmission in the presence of an osmotic factor (SLADEK et al. 1995, 1998; GORACA 1998). Microdialysis of cerebral structures has demonstrated that the release of glutamate in the region of the organum vasculosum of the lamina terminalis and median preoptic nucleus in rats is enhanced after intraperitoneal injection of hypertonic saline (ONAKA and YAGI 2001). The latter authors concluded that EAA of this cerebral region are

involved in the activation of neurosecretory neurons in the SON after osmotic stimulation. Release of both neurohormones as a result of osmotic stimulation is associated with the activation of ionotropic receptors, including both NMDA (ONAKA and YAGI 2001) and non-NMDA ones (SLADEK et al. 1998). Metabotropic receptors are not involved in this process (MORSETTE et al. 2001). Activation of an NMDA receptor by an osmotic stimulus enhances the expression of nuclear AVP RNA in SON (AMAYA et al. 1999).

Reflex OXT release due to mammary gland stimulation in female rats is also dependent on transmission in the Glu-ergic neurons at the hypothalamic level (PARKER and CROWLEY 1993a). In this reflex, the glutamate transmitter exerts its effect mainly via the AMPA and kainate receptors, but the role of NMDA receptors is also very important (PARKER and CROWLEY 1995). The interaction between norepinephrine and glutamate transmission in the SON in the milk ejection reflex has been discovered (PARKER and CROWLEY 1993b). Recent studies on hypothalamic organotypic cultures revealed that intrahypothalamic glutamatergic inputs govern synchronization of bursting firing in OXT neurons (ISRAEL et al. 2003). Such periodicity of bursting activity in OXT neurons occurs just before each milk ejection in the lactating rat.

A group of OXT neurons originating in the PVN and projecting to extrahypothalamic brain areas and spinal cord control penile erection. Excitatory amino acids activate these OXT neurons via NMDA receptors and are responsible for this sexual response. The activation of OXT neurons by excitatory amino acids is secondary to the activation of nitric oxide (NO) synthase. NO in turn activates, by a mechanism that is as yet unidentified, the release of OXT from OXT neurons in extrahypothalamic brain areas (MELIS and ARGJOLAS 2003).

CHEVALEYRE and co-workers (2002) studied the role of interplay between postsynaptic dendritic AVP/OXT release and presynaptic glutamate release in SON in the rat. *In vivo* and *in vitro* experiments showed that this interplay is required for morphological plasticity

observed during the second postnatal week in the SON in rats. NMDA receptor activation is necessary for the increase and maintenance of the dendritic arbor of the SON neurons (CHEVALEYRE et al. 2002).

Effect of excitatory amino acids on extrahypothalamic AVP-ergic neurons. The effect of EAA on the activity of AVP-ergic neurons in rabbit hippocampus was also investigated. As mentioned above, both AVP-ergic terminals (BUIJS 1978) and AVP-ergic cell bodies (HALLBECK et al. 1999) were identified in rat hippocampus, and AVP and OXT release into the fluid perfusing the hippocampus of awake rats was demonstrated (LANDGRAF et al. 1988; LANDGRAF et al. 1991). It had not been known before whether there were any AVP-ergic neurons or their terminals in the rabbit hippocampus. Recently, the release of AVP into the fluid dialyzing the hippocampus in a rabbit has been observed, which allows a conclusion indicating the presence of such terminals (ORLOWSKA-MAJDAK et al. 2003). The addition of NMDA to the fluid dialyzing the rabbit hippocampus increased the release of AVP (ORLOWSKA-MAJDAK et al. 2003). The above indicates an excitatory effect of EAA on the AVP-ergic terminals located in the hippocampus, which may play a role in the previously documented involvement of AVP and glutamates in memory-related processes (URBAN 1998).

Conclusions

Both *in vitro* and *in vivo* experiments have demonstrated that excitatory amino acids exert a direct effect on AVP- and OXT-ergic neurons, enhancing their bioelectric activity, as well as AVP and OXT release, whereas they may also exert an inhibitory effect, mediated by GABA-ergic neurons.

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