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Short Communication

Possible Role of Glutamate/Oxytocin/GABA Interactions during Motivational Stress in Sheep

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Summary

The main aim of the manuscript is to find possible correlation between Glutamic Acid (Glu) from the one hand and Oxytocin (OT) and γ-Amino Butyric Acid (GABA), from the other hand, in motivational and motor structures of Central Nervous System (CNS) under conditions of emotional stress of sheep.

Introduction

Selected CNS structures are the areas responsible for emotional states, including anxiety, fear, aggression, escape (hypothalamus, hippocampus, hypophysis, septum, and cortex frontalis) and relevant anatomical and functional motor areas (striatum, pons, medulla, cerebellum, partis lumbo-sacralis medullae spinalis). Receptors specific to Glu, OT and GABA, recently are considered as the most important neurotransmitters/neuromodulators playing a significant role in crucial for life states of danger, conflict or adaptation to continually changing living conditions, especially when the effects of harmful factors (noxa) go beyond the adaptive capacities of organisms. It may lead to pathophysiological disorders (neuron degenerations, nerve degenerations), tissue and/or organ injuries (maladaptive diseases – PSE, sudden cardiac death) and even death from exhaustion. The reasons for such disorders are not only mental and physical factors, but also chemical ones. It occurs both in foetal (prenatal life) and postnatal life, and it concerns for example excessive release of Glu in prefrontal cortex in the area of oligodendrocytes of rats [1,2]. The acid can have an excitotoxic and, particularly, neurotoxic effects on neurons, causing their degeneration and CNS degenerative diseases, what may result in nerve function disorders, embryonic deaths or foetal deaths in perinatal or postnatal period. Glu-stimulating activities in human and animal organisms are of the utmost importance, for it has been proven that, as neurotransmitter, in stressful situations it is released with high concentration [3]. As a neurotransmitter stimulating CNS, it affects target cells binding and stimulating two classes of specific receptors: via ligand-gated ion channels (ionotropic receptors- iGluR) and/or G protein-coupled receptors (metabotropic glutamate receptors- mGluR) present in all CNS and PNS (peripheral nervous system) motivational and motor structures.

Another, specified within this subject, neurotransmitter/neuromodulator in both CNS and adrenal gland structures turned out to be Oxytocin (OT). Although OT is perceived as a classic hormone circulating in blood and playing essential role during labour and lactation, it also can function as a neurotransmitter/neuromodulator via specific receptors (OTR). These receptors, just as mGluR, and the OT itself have been found in such structures as amygdala, nucleus accumbens, nucleus vagi dorsales or hippocampus [4]. They can be involved in pathophysiology of such diseases as fear, depression or schizophrenia. The results of conducted experiments suggest explicitly, that OT is a key mediator of complex emotional and social behavior, including attachment to place, social acknowledgement or aggression [5]. In addition, OT mitigates feeling of fear (has an anxiolytic-like properties) and has an alleviating effect on the symptoms of congenital fear, as well as on reward system [3,4]. The most recent studies [6] explicitly proved an increasing gene expression of OT in suprachiasmatic and paraventricular nuclei of hypothalamus under repeated stress and its role in adaptation processes. It has been also proven that microinjections of OT to brain structures reduce organism's reaction to stress stimuli [7]. It has been determined that OT has a neuroprotective effects through increasing foetus neuronal resistance to potential CNS injuries during labour, especially under conditions of foetal/infant hypoxia [8,9]. Taking into consideration its great influence on wide range of behavior, antistressoric and neuroprotective effects, therapeutic role of OT is being currently under intensive studies, also in the therapy of many neuropsychiatric disorders [10]. For it has been proven that OT intensifies general motor activity, both spontaneous and constrained one. This activity is to occur at spinal cord level [11]. This leads to the conclusion, that the investigation should confront the hypothesis about anti-stressoric effects of OT and its receptors in CNS. Independent studies have showed that both mGluR antagonists in acute intestinal stress [acute nociception; [12-14] and OT itself in adrenal glands of sheep under emotional stress prevent adrenal cortisolemia and catecholaminemia [15,16]. It confirms their opposing biological activities. It has been explicitly determined that GABA, which is the primary inhibiting transmitter in CNS and PNS with both pre- and postsynaptic effects, intensifies its neuronal activity in the presence of OT. Consequently, it can be assumed that it has also anti-stressoric effects, thus the interest of the initiators of the investigation in defining the role of GABA in CNS structures as well as in adrenal cortex and medulla of sheep, in examined intravital states of animals during postnatal period of growth.

The role of catecholamines (E, NE, DA) and indolamine (5-HT) in the context of stress and motor functions of animals and human has been repeatedly proved [17], that is why there is no need to present additional explanation and argumentation for the control of their concentration in CNS structures as well as in adrenal cortex and medulla both under stress and during adaptation period.

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Under stress, integrated Hypothalamic-Pituitary-Adrenal (HPA) reaction occurs through interaction between brain pathways sensitive to stress and neuroendocrine neurons of Paraventricular Nucleus of the hypothalamus (PVN). Stressors releasing an immediate mental anxiety (systemic stressors) are directly connected with PVN, probably via catecholaminergic (DA, NE) projections from brainstem. And to the contrary, the stressors which change behaviour and require the assessment of the nature of the stressor by higher brain structures seem to be transmitted by limbic pathways of forebrain (nuclei amygdaloides, septum, hippocampus, hypothalamus, hypophysis, and cortex frontalis). Limbic forebrain structures are connected with PVN via interaction with GABA-ergic neurons in nucleus accumbens stria terminalis, areae preopticae et hypothalamus. That is why final behavioral reaction as a result of stress is probably related to modulation of GABA-ergic activity of PVN, balancing the stimulating effects of Glu in PVN [18]. Recent functional and neuroanatomical results indicate that disease processes, as the consequence of inappropriate stress control refer to dysfunction of stress behavioral pathways [19]. Then, it can be assumed that stress neuronal pathways have a central control over hypothalamic-pituitary-adrenal axis, particularly with the participation of Glu, OT and GABA, taking into consideration its role in inhibiting PVN nucleus activity, and eventually in reducing synthesis and releasing glucocorticosteroids, as it is observed during stressor activity.

Too high concentration of glucocorticosteroids, dependent on feedback mechanism of HPA activity causes immunosuppression and unfavourable biological effects.

All these biological effects of neurohormones/neuromodulators released under stress and during adaptation are possible and occur after binding of specific individual receptors that is metabotropic glutamate receptors, oxytocin receptors and GABA ones.

The results of the studies indicating the presence of glutamic acid and OT as well as their receptors in different peripheral organs, including adrenal glands [15,20,21], suggest the possibility of their activity outside CNS, in the context of adrenal glands and their role in developing stressoric reaction intensity and adaptive capacities of animals.

As of yet it has been known, one of the most important excitatory neurotransmitters in nervous system and peripheral structures of rodents is glutamic acid. The data included in literature indicate that in mice under immobilizing stress extracellular concentration of this acid increases in medial prefrontal cortex, while in the brain of sheep foetus its excessive release has neurotoxic effects on oligodendrocytes via AMPA and NMDA receptors. At the same time in rodents, extrahormonal activity of Oxytocin (OT) in such structures as Brodmann area 28 of the cerebral cortex, hypothalamus or nucleus amygdalae was proved, then this hormone is considered as a neuromodulator, and exogenous oxytocin prevents extracellular increase of glutamic acid concentration under stress conditions.

References

1. Grassi S, Frondaroli A, Pettorossi VE. Different metabotropic glutamate receptors play opposite roles in synaptic plasticity of the rat medial vestibular nuclei. J Physiol. 2002; 543: 795-806.
2. Hascup ER, Haskup KN, Pomerleau F, Huetti P, Hojos-Korcsok E, Kehr J, et al. An allosteric modulator of metabotropic glutamate receptors (mGluR2), (+)-TEMPIP, inhibits restraint stress-induced phasic glutamate release in rat prefrontal cortex. J Neurochem. 2012; 619-627.
3. Qi J, Han WY, Yang JY, Wang LH, Dong YX, Wang F, et al. Oxytocin regulates changes of extracellular glutamate and GABA levels induced by metamphetamine in the mouse brain. Addiction Biology. 2012; 17: 758-769.
4. Rinaman L, Sherman TG, Stricker EM. Vasopressin and oxytocin in the central nervous system. 2000; 1-11.
5. Bosh OJ, Sartori SB, Singewald N, Neumann ID. Extracellular amino acid levels in the paraventricular nucleus and the central amygdala in high- and low-anxiety dams rats during maternal aggression: regulation by oxytocin. Stress. 2007; 10: 261-270.
6. Babygirija R, Zheng J, Ludwig K, Takahashi T. Central oxytocin is involved in restoring impaired gastric motility following repeated stress in mice. Am J Physiol Regul Integr Comp Physiol. 2010; 298: R157-165.
7. Cohen H, Kaplan Z, Kozlovsky N, Gidron Y, Matar MA, Zohar J. Hippocampal microinfusion of oxytocin attenuates the behavioral response to stress by means of dynamic interplay with the glucocortocoid-catechplamine responses. J Neuroendocrinol. 2010; 22: 889-904.
8. Brown CH, Grattan DR. Does maternal oxytocin protect the fetal brain? Trends Endocrinol. Metab. 2007; 18: 225-226.
9. Tyzio R, Cossart R, Khalilov I, Minlebaev M, Hubner CA, Represa A, et al. Maternal oxytocin triggers a transient inhibitory switch in GABA signaling in the fetal brain during delivery. Science. 2006; 31: 1788-1792.
10. Levin R, Edelman S, Shalev I, Ebstein RP, Heresko-Levy U. The role of oxytocin in neuropsychiatric disorders: concept and mechanisms. Ritoner MS, editor. In: Brain Protection in Schizophrenia, Mood and Cognitive Disorders. Springer. 2010; 611-635.
11. Gimpl G, Fafhrenholtz F. The oxytocin receptor system: structure, function and regulation. Physiol Rev. 2001; 81: 629-683.
12. Kania BF, Brytan M, Tomaszewska D. Centrally administered verapamil prevents the autonomic reaction to visceral pain in sheep. Res Vet Sci. 2009; 86: 121-128.
13. Kania BF, Sutiak V. Influence of centrally administered Diltiazem on behavioral responses, clinical symptoms, reticulo-ruminal contractions and plasma catecholamine level after experimentally induced duodenal distension in sheep. Res Vet Sci. 2011; 90: 291-297.
14. Kania BF, Wrońska D. Supraspinal basis of analgesic and clinical effects of the metabotropic glutamate mGluR1 antagonist during colonic distension in sheep. Small Rum Res. 2014; 117: 84-93.
15. Wrońska-Fortuna D, Frys-Żurek M, Niezgoda J. Response of the pituitary and adrenal glands of sheep subjected to restraint stress after repeated isolation stress. Bull Vet Inst Pulawy. 2009; 53: 159-167.
16. Wrońska-Fortuna D, Błachuta M, Hajduk M. The effect of ACTH on in vitro OXY release from sheep adrenal gland. 21th Molecular and physiol. aspects of regulatory processes of the organism. Cracow. 2012; 409-410.
17. Kvetnansky R, Sabban EL, Palkovits M. Catecholaminergic system in stress: structural and molecular genetics approaches. Physiol Rev. 2009; 89: 535-606.
18. Lee Y, Davis M. Role of hippocampus, the bed nucleus of the stria terminalis, and the amygdala in the excitatory effect of corticotropin-releasing hormone on the acoustic startle reflex. J Neurosci. 1997; 15: 6434-6446.
19. Herman JP, Cullinan E. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci. 1997; 20: 78-84.
20. Sarria R, Diez J, Losada J, Donate-Oliver F, Kuhn R, Grandes P. Immunocytochemical localization of metabotropic (mGluR2/3 and mGluR4a) and ionotropic (GluR2/3) glutamate receptors in adrenal medullary ganglion cells. Histol Histopathol. 2006; 21: 141-147.
21. Laferrere B, Olivan B, Bose M. Stress and obesity: the role of hypothalamus-pituitary-adrenal axis in metabolic disease. Curr Opin Endocrinol Diabetes Obes. 2009; 16: 340-346.