The Role of Oxytocin (Oxy) for Pain and Stress

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It is widely believed that a stressor, regardless of its nature, activates the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-spinal-adrenal axis (SAA). The effect of these stimulations is the increased release of adrenal glucocorticosteroids (especially cortisol) and catecholamines (epinephrine – E, norepinephrine – NE and in a lesser extent of dopamine – DA)), respectively from the cortex and adrenal medulla [1]. One of the factors triggering stress is pain, both physical, chemical and mental. However, it is known that the overall response to stressors is much more complicated and involves changes in the activity of central DA-ergic structures in both the motivational and motor systems. Changes in DA concentrations in motivational structures come to the fore. DA is released in response to psychological and physiological stress factors [2]. Nevertheless the range of concentrations secreted depends to a large extent on sex, and individual variability, including genetic differences. It turned out that OXY is also released under stress, exhibiting anxiolytic properties, and with anti-stress activity *via* OXY-R specific receptors, both centrally and peripherally [3]. Strong functional relationships between OXY- and DA-ergic systems have been researched. Increased by nociception, DA-ergic transmission in the dorsal caudate nucleus and in the globus pallidus (motor structures) is positively correlated with the intensity of pain assessed by healthy individuals [4,2]. The reaction of DA-ergic ganglia of the brain base to pain is opposite and is associated with an increase in negative interactions and anxiety during the action of the nocifensive factor [4]. The ventromedial part of the caudate nucleus receives information from numerous structures of the limbic system such as the hippocampus, amygdala, frontal visual cortex or anterior cingulate and hypothetically functions as an integrating center, receiving affective and motivational cognitive information; and regulating the occurrence of behavior [5,6]. OXY would therefore have an anti-dopaminergic and anti-stress influence [7,8]. These anxiolytic effects of OXY are mainly due to its anti-glutamatergic (anti-Glu) and anti-aspartic (anti-Asp) activity in the same motivational and motor structures in which glutamate and aspartate receptors are found, respectively [9]. It is known that Glu and Asp – especially the former – released in high concentrations during stress and pain act as the main stimulant transmitter, capable of even neurotoxic effects on neurons. Glu, by facilitating neurotransmission, increases the excitability of postsynaptic structures, which may even lead to excitotoxic effects. It also increases the ability to feel pain. OXY

– released in the same structures as Glu – prevents its depolarising effect on presynaptic elements of sensory and pain conduction structures, thus preventing depolarisation of presynaptic nerve endings and the release of stress hormones and neurotransmitters of pain sensation [10]. The molecular mechanism of these OXY interactions is basically concerned with inhibiting the release of Ca^{2+} ions from its intra-neuronal stores, and thus blocking of neuronal calcium channels and preventing them from opening, which is a necessary process for depolarising nerve endings and releasing relevant transmitters. One additional indication of the beneficial effects of endogenous OXY in pain and stress is its potential for GABAergic effects. It is a recognised inhibitory transmitter with pre- and postsynaptic activity in all brain structures. In mammals subjected to psychogenic stress, OXY is released in both the brain and the periphery [7]. Although little is still known about the role of endogenous OXY in stress biology, especially in chronic stress, its use as an exogenous substance abolishes the acute stimulation of the HPA axis in primates and rodents [6] and reduces the release of cortisol, the main mediator of the neuroendocrine stress response [10]. So these theoretical premises prompted neuroscientists to examine OXY as a pain and stress modulator; to use OXY or its agonists in clinical settings. It turned out that in male rats subjected to the stress of 10 minutes of intense swimming, the release of OXY increases by 200% (from about 2 pg/dialysate to 4 pg), Glu (from 2.2 to 6.0 pMol/30 µl dialysate), Asp (from 1.2 to 2.8 pMol/30 µl dialysate) and GABA (from 0.6 to 0.8 pMol/30 µl dialysate) in the central amygdala – the central structure controlling the processes of triggering emotions and stress response. The injection of the specific OXY antagonist, i.e. the *des*-Gly-NH$_2$*d*(CH$_2$)$_5$(Tyr(Me)^{2}Thr^4)OVT, to both amygdala structures – by reverse microdialysis – before and during swimming stress shortened the animals' drowing time by 55% and increased swimming time by 29%, respectively. Topical use of the OXY-R antagonist also significantly increased the concentration of Glu and Asp excitatory amino acids released under stress, while their release in the animal control group did not change [11]. These data provide evidence of the stimulation of the amygdala oxytocinergic system during stress response, and indicate that the mechanisms mediating via the amygdala OXY receptors are involved in triggering an anti-stress strategy, which may also rely, at least partially, on the inhibitory effect of OXY on the release of excitatory amino acids during the stress. In this regard, the role of metabotropic glutamate receptors antagonists

may not be overestimated in the clinical praxis.

Wrońska-Fortuna stated, that during the exposure of the organism to the changing impact of repeated or altered different stressors, the different amount of CRH and AVP released from the hypothalamus, and their interaction with the limbic system, directly influence the pituitary activity, and in this way they form the level of ACTH in blood plasma [3]. In this case, the level of cortisol is not sufficient for marking HPA axis activity and only reflects a peripheral rate of metabolism, which facilitates the organism's metabolic adaptation during the action of different stressors.

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