CELLULAR CONSEQUENCES OF STRESS AND DEPRESSION

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Abstract: *The brain responds to stress in a complex way, correlated with the activation and inhibition of the neurons involved in the emotional, cognitive and sensory motor processes. Stress is one of the main activators of the hypothalamic-pituitary-adrenal axis and of the adrenergic system.*

Keywords: *stress, corticosteroids, adrenalin*

Rezumat: *Creierul răspunde experienţelor stresante într-o manieră complexă corelată cu activarea şi inhibarea neuronilor implicaţi în procesele emoţionale, cognitive, autonome, motorii şi senzoriale Stressul este cunoscut a activa sistemele neurohormonale cum ar fi axa hipotalamo-pituitaro-adrenaliană şi sistemele adrenergic şi noradrenergic.*

Cuvinte cheie: *stress, corticosteroizi, adrenalina*

INTRODUCTION

Life-stressing events are among the strongest factors that can induce depression. The brain responds to stress experiences in a complex way, correlated with the activation and inhibition of the neurons involved in the emotional, cognitive, autonomous, motor and sensory processes. Chronic stress, which is known to be accompanied by the hyperactivity of neurotransmitters induces cellular changes that can be regarded as a form of plasticity. Since social stress in animals recalls the symptoms that are similar to those shown by the depressed patients, chronic social stress can serve as an experimental model to investigate the neural processes that may occur during depressive disorders in humans. The research done in the recent years reached a considerable progress in understanding the causes of depression and the neural cell mechanisms.

Stress alters the activity of the adrenergic and noradrenergic neurons. Stress is known to activate the neuronal-hormonal systems, such as the hypothalamus-pituitary-adrenalin axis, to issue "the stress peptide" of the central nervous system, the corticotrophin release factor (CRF) and the secretion of glucocorticoids from the adrenal gland. These steroids were identified as prominent factors that modify the metabolic processes, both in the body and in brain during stress and depression. (Duman)

Another key group of substances involved in speeding up the basic metabolism include adrenaline and noradrenalin.

Noradrenergic and adrenergic neurons are placed in the brain stem where it forms groups of cells that are projecting their axons in many parts of the brain. The best studied group of noradrenergic neurons, placed in the locus coeruleus, innervates certain brain regions including the neocortex and the limbic system. The limbic system is involved in the regulation of the emotional processes.

Noradrenergic neurons in the locus coeruleus play an important role in regulating the mood, the emotions and the distributive attention.

When there is such a stress stimulus, noradrenalin is released from the nerve terminations into the target brain areas, and is directed to the adrenergic receptors belonging to the group of receptors coupled with the G protein (GPCRs). They express signals from the extracellular to the intracellular compartment. GPCR signals require several levels of transmission that last from milliseconds to minutes. The link between adrenaline, noradrenalin and receptors initiates a cascade of intracellular events that lead to the cell activity and involves enzymes (adenylate cyclase phospholipase, kinases and phosphatase), secondary messengers (adenosine-mono-phosphate-cyclic - AMPc, guanosine-mono-phosphate - GMPc, calcium ions, diacylglycerol - DAG and inosytol-phosphates - IP) and ionic channels that modulate the electrical activity of the neuron.

A long-term effect that occurs a few minutes after the GPCR regulation is the regulation of the transcription and translation. (Squire et al.)

Noradrenergic neurons from the locus coeruleus are projected in the limbic and cortical areas but also in the thalamus, cerebellum and spinal cord. They play an important part in the regulation of mood and attention. Other groups of noradrenergic neurons, belonging to the A1, A2, A5 and A7 cellular groups are projected to more restricted regions, playing an important part in the autonomic function.

There are different types of adrenergic receptors in the brain, whose activation may stimulate or inhibit the respective target neurons. Adrenalin and noradrenalin are coupled to the same types of adrenergic receptors, although there are differences of affinity.

Various experiments have shown that during stress, the adrenergic and noradrenergic neurons released more adrenaline and noradrenalin, and that the turnover of

these neurotransmitters is accelerated, so that their concentrations and/or quantity of their metabolites fluctuate in relation to the intensity and duration of stress. Acute stress induces only a transient increase in the levels of noradrenalin, but chronic stress can lead to repetitive increases in concentration.

As a result, the adrenoreceptors from the target neurons surface are bombarded with noradrenalin, bringing about a reduction in the adrenal receptors number (receptor downregulation). On the other hand, low concentrations of noradrenalin induce the increase in the adrenal receptors (receptor up-regulation). (Ribas et al.)

The most studied receptors in connection with the regulation in chronic stress are the adrenergic receptors type alfa2, which have three known subtypes A, B and C.

Because of the brain spread distribution, alfa2 adrenergic receptors are involved in different ways in the meditation of the sedatives and analgesics effects of agonists, such as dexmedetomidine and in baroreceptor reflex modulation. The involvement of alfa2-ARS in the regulation of attention is suggested by the fact that methylphenidat**,** (a non stimulated amphetamine used to treat children with hyperactivity disorder and attention deficit), affects the neural activity of the locus coeruleus. Modifications of cerebral alfa2AR were absent in the depressed patients.

Adrenergic alfa2A autoreceptors of the noradrenergic neurons from the locus coeruleus modulate the noradrenalin release via negative feedback. (Kable et al.)

The expression of this auto-receptor is reduced immediately after the onset of stress. Regarding addiction, alfa2A-ARS is also expressed in the neurons that release the excitatory neurotransmitter glutamate. (Meyer et al.) Various forms of stress, such as immobilization or cold environment, change the alfa2-AR number in distinct brain regions. Psychosocial chronic stress reduces the expression of alfa2-AR in the brain regions that regulate the autonomous functions and the emotional behaviour. This decrease in the number of receptors is more likely to be correlated with increased levels of noradrenalin due to stress. Adjusting the release of noradrenalin is disrupted immediately after the onset of stress, as it may be observed when reducing the expression of alfa2a-AR in the locus coeruleus. After several weeks of stress, we initially observe a high level of noradrenalin and finally a low level in the prefrontal cortex, a brain region important in mood and behaviour regulation. After a period of chronic stress, the levels of noradrenalin are obviously low in the whole brain, probably because of a gradually deficit achieved in the neurotransmitter synthesis, in the transportation and/or release from neurons noradrenergic. (Flugge et al.) Postmortem studies on the brains of the patients with depression have revealed a decrease in the number of alfa2 adrenergic receptors in different regions of the brain. These data support the hypothesis deficit of noradrenalin.

Beta adrenergic receptors are also changed during stress. They are present in neurons and glial cells. Stress decreases the number of beta-ARS in the brain. The number of beta1-ARS in the frontal and temporal cortex of the patients deceased by suicide was found significantly lower compared to the normal control group. Flugge et al. have noticed that 4 weeks after psychosocial stress, the number of beta1-ARS was reduced in the hippocampus cells and in the parietal cortex.

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