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Streszczenie rozprawy doktorskiej mgr Joanny Bernackiej pt. „Noradrenergic regulation of dopamine release in the mesolimbic system: receptor mechanisms in the ventral tegmental area and their modulation by stress"

The dopaminergic and noradrenergic systems are involved in numerous functions as well as pathologies in the central nervous system. Furthermore, these systems interact with each other in various brain structures. Of particular importance for the interaction between these systems is the midbrain ventral tegmental area (VTA). Dopamine release from the VTA to forebrain structures is associated with reward and associative learning processes, playing a crucial role in addiction and neuropsychiatric diseases related to stress. Noradrenergic signaling in the VTA is a putative mechanism involved in this interaction. It is of special interest due to the fact that noradrenaline, among its other roles, is also a fundamental mediator of stress responses. In particular, noradrenergic receptors in the VTA play a large role in the interaction between the noradrenergic and dopaminergic systems, modulating local neuronal activity and consequently, dopamine release in the forebrain.

On this basis, we formulated the following hypotheses: a) noradrenaline released in the VTA, through catecholamine receptors, regulates dopamine release in the forebrain, subsequently influencing processes dependent on their activity, b) environmental stimuli, such as acute stress, can affect the interactions of the dopaminergic and noradrenergic systems, leading to behavioral effects. The primary objective of this doctoral dissertation was to investigate the influence of noradrenergic receptor activity in the VTA on the phasic release of dopamine to nucleus accumbens (NAc) and basolateral amygdala (BLA). It also aimed to determine how stress might modulate these regulatory mechanisms.

Electrochemical studies using fast-scan cyclic voltammetry (FSCV) combined with pharmacological blockade of noradrenergic receptors in the VTA revealed that local administration of a specific α_{2A} noradrenergic receptor antagonist (BRL-44408) attenuates dopamine release in the NAc, an effect suppressed by prior blockade of D_2 dopamine receptors. Conversely, JP-1302 and imiloxan (specific antagonists for α_{2B} and α_{2C} receptors, respectively) did not affect dopamine release in the NAc.

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We then examined how animal exposure to a stressor affects noradrenergic modulation of dopamine levels in the BLA. Our FSCV recordings revealed that dopamine release in the BLA, evoked by electrical stimulation of the VTA, was regulated by both α_1- and α_2-adrenergic receptors in this structure. Exposure to a stressor weakened the impact of α_2-adrenergic receptor blockade (RX-821002) in the VTA on dopamine release to the BLA 24 hours post-stress, while stress did not influence the action of the α_1-adrenergic receptor antagonist, terazosin.

This stress-induced adaptation led us to explore the effect of α_2 receptor blockade in the VTA on fear conditioning. Using high-performance liquid chromatography, we demonstrated that the fear conditioning procedure induces elevated noradrenaline levels in the VTA. Local α_2-adrenergic receptor antagonist RX-821002, infused into the VTA before fear conditioning, weakened freezing responses during fear memory retrieval.

Taken together, these results indicate that both α_1- and α_2-adrenergic receptors influence dopamine release levels in the NAc and BLA. Furthermore, the α_{2A} subtype of noradrenergic receptors plays a primary role in regulating noradrenaline levels in the VTA and, consequently, dopamine release to the forebrain. Moreover, the modulatory effect of α_2-adrenergic receptors is altered by stress exposure and plays a role in fear memory acquisition. These findings suggest novel regulatory mechanisms through which noradrenaline can influence the mesolimbic dopaminergic system and modulate dopaminergic signaling associated with learning and memory processes.

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