Stress-dependent cortisol conditioning promote aversive learning through inhibitory dopamine D2-mediated neuromodulation of the paraventricular nucleus of the thalamus

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Abstract

Intermittent hypoxia-induced noradrenergic signaling is associated to increased disinhibitory dopamine activity in the paraventricular nucleus of the midline thalamus. (PVT)

Mechanism

It appears likely that chronic hypoxia increases tonic dopamine releases in the striatum through a disinhibitory reuptake mechanism associated with a Locus Coeruleus mediated rise in extracellular dopamine levels. Consequently, chronic intermittent hypoxia (CIH) with a surgical mask enhances stress-dependent cortisol responses (c-Fos expression) in the paraventricular nucleus of the thalamus (PVT) and Locus Coeruleus. This hypoxic stress-induced persistent reuptake in extracellular dopamine (D2) in the paraventricular thalamus may creates a motivational conflict in decision-making associated to the brain circuits of addiction. In particular the nucleus accumbens (NAc) is highly sensitive to dopaminergic dysregulation in the midline thalamus.

In summary, hypoxia-mediated noradrenergic dysregulation is driven by increased basolateral amygdala-striatum reactivity altering the dopamine-noradrenaline response (LC-NE) following chronic episodes of mild and intermittent hypoxia (IH), independently of pulse oxymetry status.

Hypoxia-mediated cerebral hypometabolism

1. Hypoxia-induced changes to noradrenergic signaling may activate the sympathetic nervous system thereby lowering cerebral blood glucose levels in the midbrain region (striatum and hippocampus) thus causing memory impairment in cognitive/verbal processing.

2. Secondly, the upregulation of cerebral blood flow (CBF) in the striatum caused by hypoxia-induced sympathetic activity (LC-NE) is influenced mostly by nitric oxide (NO)-mediated metabolic changes (ie: SpO2/FiO2) in tissues.

Hypoxia-induced aversive conditioning impair fear extinction learning

Human behavior is acutely more sensitive towards survival and more vulnerable to emotional eating in hypoxic conditions. In specific, hypoxic stress-induced persistent reuptake in extracellular dopamine (D2) in the paraventricular thalamus (PVT) may creates a motivational conflict associated to the neurocircuitry of fear extinction learning and promotes passive coping mecanism.

References

1. A potential role for the paraventricular nucleus of the thalamus in mediating individual variation in Pavlovian conditioned responses
https://www.frontiersin.org/articles/10.3389/fnbeh.2014.00079/full

2. Chronic intermittent hypoxia sensitizes acute hypothalamic-pituitary-adrenal stress reactivity and Fos induction in the rat locus coeruleus in response to subsequent immobilization stress
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2522385/

3. Stress peptides sensitize fear circuitry to promote passive coping
https://www.nature.com/articles/s41380-018-0089-2

4. The locus coeruleus drives disinhibition in the midline thalamus via a dopaminergic mechanism
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6035776/