



Stress-dependent cortisol modulation promote avoidance conditioning through inhibitory dopamine activity in the striatum.

Jack Bortone

jack@open-neurosecurity.org

Last update: April 28, 2021

## **Abstract**

Chronic intermittent hypoxia (CIH)-induced noradrenergic dysregulation is associated to increased disinhibitory dopamine activity in the paraventricular nucleus of the thalamus (PVT). Secondly, chronic hypoxic stress may increases cortisol production through a disinhibitory reuptake mechanism associated with a locus coeruleus (LC-NE)-mediated rise in extracellular dopamine levels in the dorsal striatum. Consequently, chronic intermittent hypoxia (CIH) may enhances stress-dependent cortisol responses (c-Fos expression) in the striatum through dopaminergic projections from the locus coeruleus.

## **Hypoxia-mediated cerebral hypometabolism**

Hypoxia-induced changes to noradrenergic signaling may modulate the sympathetic nervous system thereby altering cerebral blood glucose levels in the midbrain region (ventral striatum and hippocampus). Secondly, the

upregulation of cerebral blood flow (CBF) in the striatum caused by hypoxia-induced sympathetic overactivity is influenced by nitric oxide (NO)-mediated metabolic changes (ie: SpO<sub>2</sub>/FiO<sub>2</sub>) in tissues.

### **Stress-induced instrumental conditioning**

The persistent stress-induced dopamine (D<sub>2</sub>) modulation in the PVT may create a motivational conflict associated to the neurocircuitry of fear extinction learning and may promote passive avoidance mechanism in the striatum. Moreover, the human PVT is connected with the nucleus accumbens to mediate aversive conditioning and reward-motivated learning by stimulating phasic dopamine D<sub>2</sub> expression.

### **Effects of chronic social stress in womens experiencing intimate partner violence (IPV)**

Social isolation (SI) may promote inhibitory control of fear extinction memory and reinforce passive avoidance mechanisms in womens experiencing intimate partner violence (IPV). Likewise, chronic stress may enhance avoidance conditioning through the persistent modulation of locus coeruleus (LC) activity thereby increasing cortisol levels.

### **Conclusion**

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.

In specific, stress-dependent cortisol modulation of the striatum may promotes aversive and instrumental coping mechanisms through inhibitory connectivity from the locus coeruleus and paraventricular thalamus.

---

## References

1. Haight Joshua, Flagel Shelly. (2014). A potential role for the paraventricular nucleus of the thalamus in mediating individual variation in Pavlovian conditioned responses. *Frontiers in Behavioral Neuroscience* 8, 79 doi: 10.3389/fnbeh.2014.00079
2. Ma, S., Mifflin, S. W., Cunningham, J. T., & Morilak, D. A. (2008). Chronic intermittent hypoxia sensitizes acute hypothalamic-pituitary-adrenal stress reactivity and Fos induction in the rat locus coeruleus in response to subsequent immobilization stress. *Neuroscience*, 154(4), 1639–1647. <https://doi.org/10.1016/j.neuroscience.2008.04.068>
3. Pliota, P., Böhm, V., Grössl, F. *et al.* Stress peptides sensitize fear circuitry to promote passive coping. *Mol Psychiatry* **25**, 428–441 (2020). <https://doi.org/10.1038/s41380-018-0089-2>
4. Beas, B. S., Wright, B. J., Skirzewski, M., Leng, Y., Hyun, J. H., Koita, O., Ringelberg, N., Kwon, H. B., Buonanno, A., & Penzo, M. A. (2018). The locus coeruleus drives disinhibition in the midline thalamus via a dopaminergic mechanism. *Nature neuroscience*, 21(7), 963–973. <https://doi.org/10.1038/s41593-018-0167-4>
5. James M. Otis, ManHua Zhu, Vijay M.K. Namboodiri, Cory A. Cook, Oksana Kosyk, Ana M. Matan, Rose Ying, Yoshiko Hashikawa, Koichi Hashikawa, Ivan Trujillo-Pisanty, Jiami Guo, Randall L. Ung, Jose Rodriguez-Romaguera, E.S. Anton, Garret D. Stuber. (2019). Paraventricular Thalamus Projection Neurons Integrate Cortical and Hypothalamic Signals for Cue-Reward Processing. *Neuron*, Volume 103, Issue 3, 423-431.e4. <https://doi.org/10.1016/j.neuron.2019.05.018>
6. Oleson EB, Gentry RN, Chioma VC, Cheer JF. Subsecond dopamine release in the nucleus accumbens predicts conditioned punishment and its successful avoidance. *J*

Neurosci. 2012 Oct 17;32(42):14804-8. doi: 10.1523/JNEUROSCI.3087-12.2012. PMID: 23077064; PMCID: PMC3498047.