The electrophysiological dynamics of serotonin in the Lateral Habenula

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Introduction:

The Lateral Habenula (LHb) is an anti-reward centre in the epithalamus(1). Burst firing in the LHb is elevated in depression and suppressed by the anti-depressant ketamine(2).
Serotonin (5-HT) is a neuromodulator associated with the mechanism of traditional antidepressants (SSRIs)(3). It's possible, therefore, that 5-HT exerts antidepressant effects via the LHb.

Methods:

Coronal brain slices were taken from C57BL6 mice (Male, 6-12 weeks) following euthanasia with sodium pentobarbital. Slices were placed in a submerged chamber which was continuously perfused with oxygenated 'Recording Solution' at physiological temperature. Recordings were made with micro-pipettes via the Multiclamp 700B amplifier and pClamp10 software.

Results:

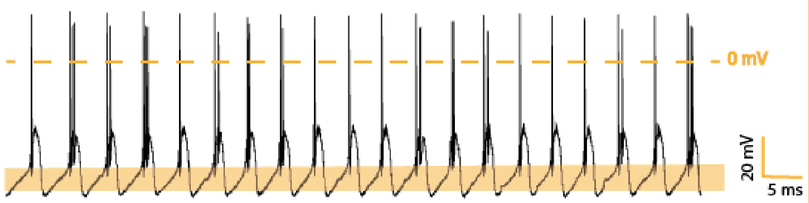

Figure 1: Raw current clamp trace of a spontaneously burst firing LHb neurone

Bursting neurones have a resting membrane potential (RMP) between -55 mV and -65 mV (Goldilocks Zone, highlighted orange). Perturbance of these neurones may push their RMP out of this zone, thus inhibiting burst firing, and alleviating depression.

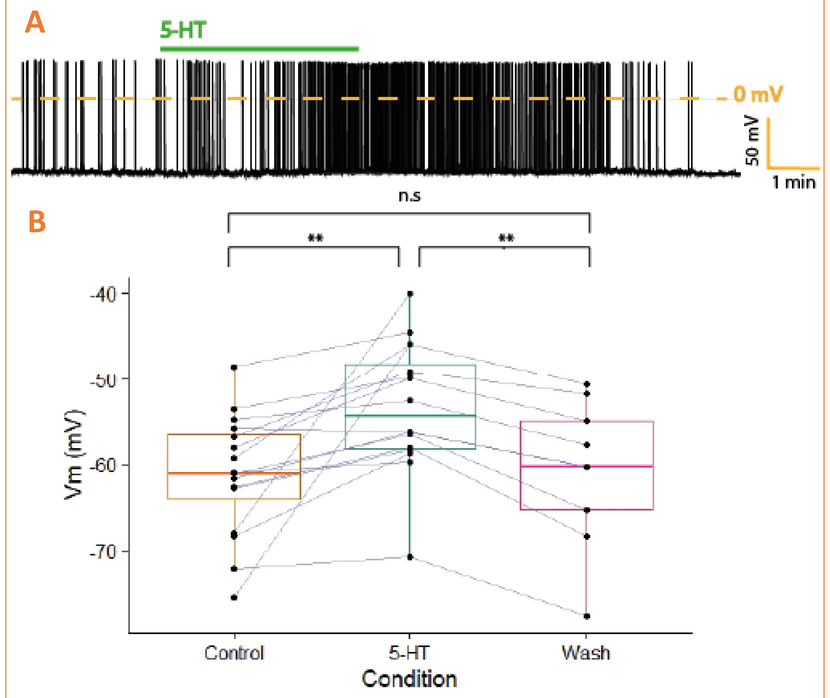

Figure 2: 5-HT exerts a depolarising effect on LHb neurones (** = p < 0.01)

5-HT has an excitatory effect in the LHb, causing a significant reversible depolarisation of LHb neurones (n = 16; p < 0.001; ANOVA; F = 10.7; *fig 2B*). This can cause a pro-depressant increase in action potential frequency (*fig 2A*)

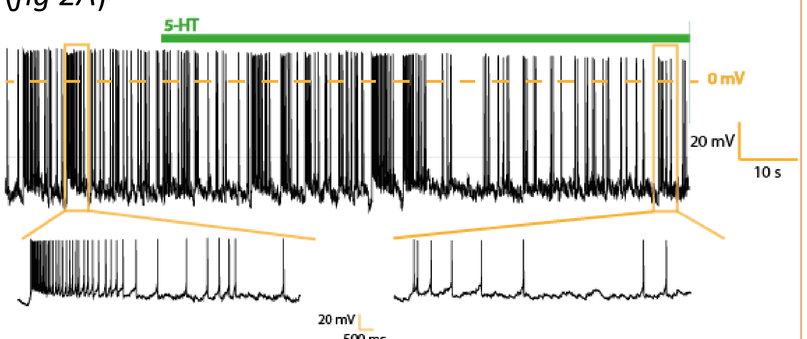

Figure 3: 5-HT can cause a shift in neuronal firing from bursting to tonic.

By depolarising LHb neurones, 5-HT can shift their RMP out of the goldilocks zone, thus inhibiting burst firing.

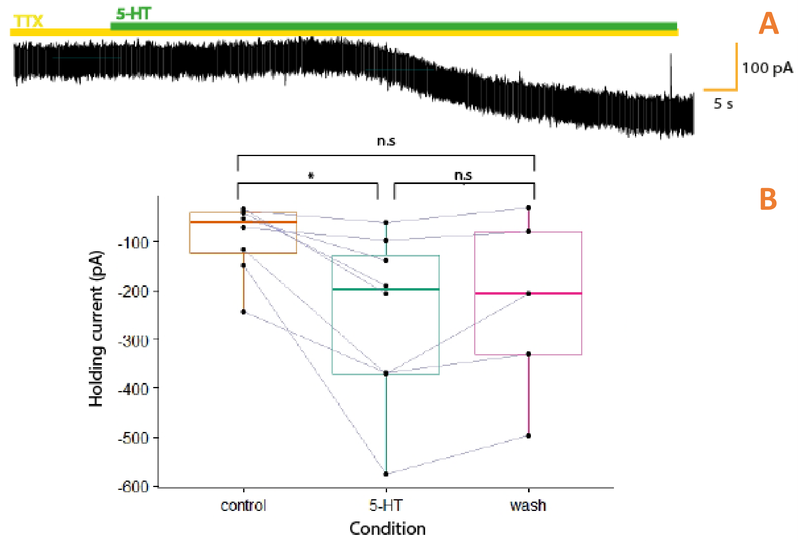

Figure 4: 5-HT causes an inward current in LHb neurones in the presence of TTX (* = p <0.05)

5-HT triggers a substantial and irreversible inward current in LHb neurones, likely underpinning observed depolarisation (n = 8; p < 0.05; ANOVA; F = 4.3; *fig 4B).* This occurs with TTX, indicating postsynaptic 5-HT receptors are responsible for this current.

Discussion:

This work shows 5-HT to trigger depolarisations in LHb neurones. The consequences of this depends on the neurone's basal state. Depolarising quiescent neurones, or low frequency tonic firing neurones, increases action potential frequency and exerts a pro-depressant effect. Depolarising burst firing cells can push RMP out of the Goldilock's Zone, thus inhibiting bursting to exert an antidepressant effect. This variability in 5-HTs effects could explain the similar variability in SSRI efficacy.

1) Cerniauskas I, Winterer J, de Jonh JW, Lukacosovich D, Yang H, Khan F, et al. Chronic Stress Induces Activity, Synaptic, and Transcriptional Remodeling of the Lateral Habenula Associated with Deficits in Motivated Behaviours Neuron. 2019;104:899-915.
2) Yang Y, Cui Y, Sang K, Dong Y, Ni Z, Ma S, et al. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. Nature. 2018;554:317-22.
3) Carhart-Harris, R. L. & Nutt, D. J., 2017. Serotonin and brain function: a tale of two receptors. Journal of Psychopharmacology , 31(9), pp. 1091-1120.