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Molecular mechanisms of appetite control via 5-HT1B receptors

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Appetite is a complex form of behaviour controlled by diverse neuronal populations of the Central Nervous System. Two of the most important of these are neurons within the arcuate nucleus of the hypothalamus that produce the potent hunger neuropeptide agouti-related protein (AgRP) and neighbouring neurons that produce satiety stimulating pro-opiomelanocortin (POMC)[(1)]. It is important not to feel both hungry and full at the same time so that it is clear whether to eat or stop eating. To prevent this, AgRP neurons send inhibitory synapses to POMC neurons utilizing g-aminobutyric acid (GABA) as a neurotransmitter. Thus, when AgRP neurons are active and stimulate hunger, they also inhibit satiety POMC neurons. However, molecular mechanisms controlling the AgRP-POMC interplay have yet to be fully clarified.

In our work we studied the impact of serotonin 1B metabotropic receptors (5-HT1BRs) on inhibitory signalling in AgRP→POMC synapses. 5-HT1BRs are involved into regulation of feeding behaviour, inhibit AgRP neurons and disinhibit POMC neurons[(1,2)]. Moreover, 5-HT1BRs impact neurotransmitter release in synapses via downregulation of voltage-gated Ca^{2+} channels (VGCCs) in hippocampal neurons[(3)]. Therefore, we set out to clarify if 5-HT1BRs regulate the level of inhibition of POMC neurons by AgRP cells and, if yes, whether this is due to 5-HT1BRs impact on VGCCs.

To achieve this, we used cellular and molecular electrophysiology targeting murine AgRP neurons labelled with GFP fluorescence.

To quantify the impact of 5-HT1BRs on neurotransmitter release in AgRP cells we recorded fluctuations of a whole-cell membrane electrical capacitance following the series of electrical stimuli delivered to hypothalamic neural tissue. The increase of membrane electrical capacitance is because neurotransmitter vesicles fuse with the cell membrane and thus release neurotransmitter into synaptic cleft. In an initial experiment, we found that activation of 5-HT1BRs with selective agonist CP-93129 results in significant reduction of the area under the curve of membrane capacitance fluctuations (AUC): to 47.6 ± 13.4% of control, $P < 0.01$, Student's t-test. Next, we tested the effect of CP-93129 on electrical charge transfer through VGCCs. Surprisingly, we found that CP-93129 downregulates charge transfer to the level sufficient for reduction of resulting AUC to ~50% of control only after series of electrical stimuli, but not in silent tissue. Continuing our work, we found that concomitant activation of glutamate receptors of AMPA type (AMPARs) in silent tissue is necessary to reproduce the CP-93129 effect on VGCCs after electrical stimulation, with subsequent AUC reduction to 42.3 ± 11.2% of control ($P < 0.01$): the level which is statistically indistinguishable from that observed in an initial experiment.

Our results suggest involvement of AMPARs into VGCC modulation in AgRP cells (as was shown earlier in a different neuron type)[(4)] and a complex mechanism controlling appetite via the AgRP→POMC synapses involving activation of AMPARs and triggered by 5-HT1BRs.

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