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SYNAPTIC TRANSMISSION

Changing the (potassium) channel?

The lipid signalling mechanisms that influence neuronal excitability are not well understood. Gantz and Bean show that the endocannabinoid 2-arachidonoylglycerol (2-AG; a lipid signalling molecule) can affect the intrinsic excitability of midbrain dopamine neurons through direct influence on the A-type potassium current (I_A).

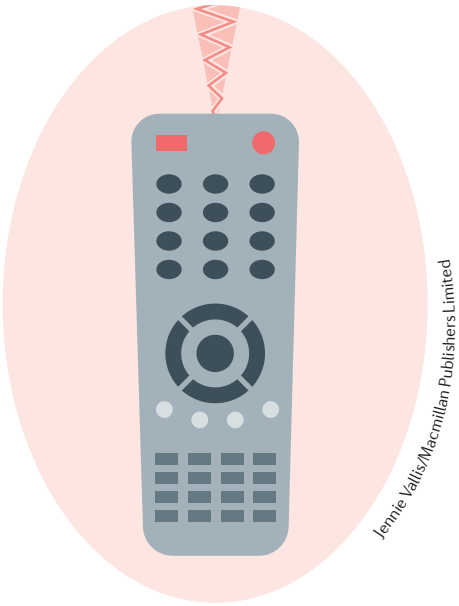
The authors used acutely isolated dopamine neurons from mouse substantia nigra pars compacta (SNc), which exhibit tonic firing. *In vivo*, these neurons also exhibit bursts of higher-frequency activity in response to reward-related cues. *Ex vivo*, application of 2-AG increased both the rate of intrinsic firing activity and the rate of current-injection-evoked activity. The increase in firing frequency resulted from decreased afterhyperpolarization along with more rapid depolarization to the next action potential.

Midbrain dopamine neurons have a strong I_A that is mediated by voltage-gated Kv4.3 channels, which contributes to their slow rhythmic firing; a reduction in I_A increases the firing rate. Application of 2-AG reduced the peak amplitude of I_A and caused faster inactivation. The modulation of I_A by 2-AG is likely to underlie the increase in dopamine neuron firing rate, an effect mimicked by pharmacological reduction of I_A.

In the brain, endocannabinoids such as 2-AG influence neurons mainly by acting on the cannabinoid receptor 1 (CB1) and CB2. Midbrain dopamine neurons express CB2s, but, interestingly, both the 2-AG-mediated decrease in I_A peak amplitude and accelerated inactivation kinetics were not affected by blockade of CBs. This suggests that 2-AG acts via a CB-independent mechanism.

A direct action of 2-AG on Kv4.3 channels was supported by effects of bovine serum albumin (BSA) added to the external saline. BSA, which sequesters 2-AG and related fatty acids from the plasma membrane, rapidly reversed the effects of 2-AG.

In dopamine neurons, activation of metabotropic glutamate receptors (mGluRs), orexin receptors or neurotensin receptors results in increased activation of phospholipase C (PLC), which in turn results in the release of 2-AG. Artificially stimulating each of these three receptors inhibited I_A. This effect was unaffected by blockade of CBs but was blocked by inclusion of BSA in the external saline, implying that 2-AG interacts directly with I_A channels.



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Blocking endogenous 2-AG synthesis or blocking PLC production prevented the inhibition of I_A following stimulation of mGluR, orexin receptors or neurotensin receptors, but this could be rescued by application of exogenous 2-AG. Overall, these data suggest that, in mouse midbrain dopamine neurons, tonic and evoked activity can be modulated by a direct interaction between the I_A and the lipid mediator 2-AG, which is produced following activation of mGluR, orexin receptors and neurotensin receptors.

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> “2-AG interacts directly with I_A channels”

ORIGINAL ARTICLE Gantz, S. C. & Bean B. P. Cell-autonomous excitation of midbrain dopamine neurons by endocannabinoid-dependent lipid signaling. *Neuron* http://dx.doi.org/10.1016/j.neuron.2017.02.025 (2017)