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Regulation of raphe serotonin neurons by serotonin 1A and 2B receptors

Arnauld Belmer* and Luc Maroteaux

Several lines of evidence implicate serotonin (5-hydroxytryptamine, 5-HT) in the etiology of mood disorders including major depressive disorders. Serotonergic neurons have long been recognized as key contributors to the regulation of mood and anxiety as the main target of serotonin selective reuptake inhibitor (SSRI) antidepressants. The therapeutic effects of SSRIs are initially triggered by blockade of the serotonin transporter SERT increasing local extracellular serotonin. Serotonin neurotransmission is tightly regulated by autoreceptors (serotonin receptors expressed by serotonin neurons) known to act through negative feedback inhibition at the cell bodies (5-HT_{1A} receptors) of the raphe nuclei or at the axon terminals (5-HT_{1B} receptors). Beneficial SSRI effects rely on long-term adaptations that are, at least partially, ascribed to a selective desensitization of somatodendritic 5-HT_{1A} autoreceptors (Richardson-Jones *et al*, 2010).

A positive regulation of serotonergic neurons by 5-HT_{2B} receptors has been detected in mice. Local agonist-stimulation of 5-HT_{2B} receptors in dorsal raphe nuclei increased extracellular serotonin suggesting a functional role of this receptor within serotonergic neurons (Doly *et al*, 2008). Expression of 5-HT_{2B} receptors has been detected in subset of serotonergic neurons albeit at low levels (Diaz *et al*, 2012). Both acute and long-term behavioral and neurogenic effects of SSRIs are abolished in mice knockout for 5-HT_{2B} receptor gene, (*Htr2b*$^{-/-}$) or after exposure to selective 5-HT_{2B}-receptor antagonists. Conversely, chronic stimulation of 5-HT_{2B} receptors by selective agonists mimicked chronic SSRI actions on behavior and hippocampal neurogenesis, which were abolished in *Htr2b*$^{-/-}$ mice (Diaz *et al*, 2012). Comparable lack of SSRI effects was recently reported in mice knockout for 5-HT_{2B} receptors only in serotonergic neurons (*Htr2b*$^{5\text{-}HTKO}$ mice), in which dorsal raphe serotonin neurons displayed a reduced firing frequency, and a stronger hypothermic effect following 5-HT_{1A}-autoreceptor stimulation (Belmer *et al*, 2018). Cell autonomous effects were confirmed by the increased excitability of serotonergic neurons observed upon raphe-selective 5-HT_{2B}-receptor overexpression. Correlative findings have been described in Humans, in which expression of 5-HT_{2B} receptors can be found in brain stem and a loss-of-function polymorphism of 5-HT_{2B} receptors has been associated with serotonin-dependent phenotypes including increased impulsivity and suicidality (Bevilacqua *et al*, 2010).

Serotonin released within raphe nuclei is known to induce feedback inhibition of serotonergic neuron firing activity by stimulating dendritic 5-HT_{1A} negative autoreceptors. Unlike soma and terminals, the dendritic serotonin release is independent of action potentials, relies on L-type Ca2+ channels, can be induced by NMDA, and displays distinct sensitivity to the SSRI antidepressants (Colgan *et al*, 2012). Dendritic serotonin release, and hence 5-HT_{1A} receptor-mediated autoinhibition, is thus engaged by excitatory glutamatergic inputs to the dorsal raphe, via locally triggered calcium influx, rather than by neuronal firing. The unique control of dendritic serotonin release has important implications for the antidepressant action of SSRIs. The lack of 5-HT_{2B} receptor in serotonergic neurons is associated with a higher 5-HT_{1A}-autoreceptor reactivity and thus a lower activity of these neurons (Belmer *et al*, 2018). The excess of inhibitory control exerted by 5-HT_{1A} receptors in *Htr2b*$^{5\text{-}HTKO}$ mice may thus explain the lack of response to chronic SSRI in these mice.

The serotonergic tone of raphe neurons and thus the SSRI therapeutic effects

likely results from the opposite control exerted by 5-HT_{1A} and 5-HT_{2B} receptors via a mechanism that remains to be described.

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