Animal Model

Tryptophan Hydroxylase 1 Knockout Mice as a Tool to Study the Function of Serotonin

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Abstract

Challenge

Serotonin [5-hydroxytryptamine (5-HT)], a neurotransmitter in the central nervous system, is known to modulate many behavioural functions such as mood. However, in the periphery it functions as a hormone and regulates vascular tone, gut motility, primary hemostasis and cell-mediated immune responses. Tryptophan hydroxylase (TPH) is the rate-limiting enzyme of serotonin biosynthesis. Lately is has been discovered that there are two different isoenzymes, TPH1 and TPH2, where TPH1 functions in the periphery and TPH2 in the central nervous system. A knockout mouse deficient in the TPH1 gene was generated to shed light on the physiological impact of serotonin in the periphery.

Technology

To investigate the multitude of physiological effects of serotonin in the periphery a knockout mouse selectively deficient in TPH1 has been generated. Studies on this animal model showed, that mice lacking TPH expression in the periphery exhibit decreased peripheral levels of serotonin and are less susceptible for thrombosis. Moreover, a receptor-independent signalling pathway in platelets named ‘serotonylation’ has been discovered, which might be a general pathway of 5-HT action. Hence, these animals offer the opportunity for further investigations on signalling events initiated by 5-HT. Furthermore, due to the duality of the serotonin system this animal model opens new avenues for specific therapeutic approaches exclusively affecting the peripheral or central 5-HT actions such as for thrombotic or psychiatric diseases, respectively. Moreover, TPH1-deficient mice are a suitable model for reconsideration of findings about 5-HT after the duality of the system has been discovered.
Schematic representation of the duality of the serotonergic system. Serotonin is synthesised by two distinct TPH enzymes in the brain (TPH2) and in the periphery (TPH1). Thus, the indicated peripheral and central functions of serotonin are differentially regulated and can be targeted independently. Only in the pathogenesis of migraine, serotonin from both sources may be involved. Source: Walther et al.

Commercial Opportunity

Breeding pairs are available under Tangible Property Licence Agreement.

Further Reading

- Walther et al., 2003a, Science, 299, 76.
- Walther et al., 2003b, Cell, 115, 851-862.
- Walther and Bader, 2003c, Biochem. Pharmacol. 66: 1673-1680.

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