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REVIEW

Cardiovascular remodeling and the peripheral serotonergic system

Remodelage cardiovasculaire et système sérotoninergique périphérique

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Summary Plasma 5-hydroxytryptamine (5-HT; serotonin), released from blood platelets, plays a major role in the human cardiovascular system. Besides the effect of endogenous serotonin, many drugs targeting serotonergic receptors are widely used in the general population (antiobesity agents, antidepressants, antipsychotics, antimigraine agents), and may enhance the cardiovascular risk. Depending on the type of serotonin receptor activated and its location, the use of these compounds triggers acute and chronic effects. The acute cardiovascular response to 5-HT, named the Bezold-Jarish reflex, leads to intense bradycardia associated with atrioventricular block, and involves 5-HT_3, $5\text{-HT}_{1B/1D}$, 5-HT_7 and $5\text{-HT}_{2A/2B}$ receptors. The chronic contribution of 5-HT and its receptors (5-HT_4 and $5\text{-HT}_{2A/2B}$) in cardiovascular tissue remodeling, with a particular emphasis on cardiac hypertrophy, fibrosis and valve degeneration, will be explored in this review. Finally, through the analysis of the effects of sarpogrelate, some new aspects of 5-HT_{2A} receptor pharmacology in vasomotor tone regulation and the interaction between endothelial and smooth muscle cells will also be discussed. The aim of this

Abbreviations: 5-HIAA, 5-hydroxyindole acetic acid; 5-HT, 5-hydroxytryptamine (serotonin); eNOS, endothelial nitric oxide synthase; MAO-A, monoamine oxidase A; NO, nitric oxide; SERT, serotonin transporter; TGF, transforming growth factor.

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review is to emphasize the cardiac side effects caused by serotonin receptor activation, and to highlight their possible prevention by the development of new drugs targeting this system.

MOTS CLÉS
Sérotonine ;
Remodelage cardiaque ;
Hypertrophie cardiaque ;
Dégénérescence valvulaire ;
Fibrose

Résumé La sérotonine (5-hydroxytryptamine ou 5-HT) plasmatique, libérée dans la circulation générale par les plaquettes sanguines, joue un rôle majeur dans le système cardiovasculaire humain. En plus des effets produits par la sérotonine endogène, de nombreux médicaments ciblant les récepteurs sérotoninergiques (antiobésité, antimigraineux, antipsychotiques, antidépresseurs...) sont largement utilisés dans la population générale et pourraient augmenter le risque cardiovasculaire. En fonction du sous-type de récepteur activé et de sa localisation, l'utilisation de ces produits induit des effets aigus et chroniques. L'effet cardiovasculaire aigu du à la sérotonine, appelé réflexe de Bezold-Jarish et conduisant à une bradycardie intense associée à un bloc atrio-ventriculaire, implique les récepteurs sérotoninergiques 5-HT_3, 5-$HT_{1B/1D}$, 5-HT_7 et 5-$HT_{2A/2B}$. La stimulation chronique des récepteurs 5-HT_4 et 5-$HT_{2A/2B}$ conduit au remodelage du tissu cardiovasculaire, et en particulier les aspects d'hypertrophie cardiaque, de fibrose et de dégénérescence valvulaire ont été développés dans cette revue. À travers les effets du sarpogrelate, de nouveaux aspects de la pharmacologie du récepteur 5-HT_{2A} dans la régulation du tonus vasomoteur et l'interaction entre les cellules endothéliales et les cellules musculaires lisses sont aussi discutés. Le but de cette revue est de souligner les effets indésirables cardiovasculaires liés à la stimulation des récepteurs sérotoninergiques périphériques dans le but de les prévenir mais aussi de mettre en avant les possibilités offertes par le développement de nouvelles molécules ciblant ce système.

Background

Outside the area of migraine and the use of 5-$HT_{1B/1D}$ serotonergic agonists, some recent clinical observations have revived interest in and questions about serotonin (5-hydroxtryptamine [5-HT]) and its receptors in the cardiovascular field. The induction of pulmonary hypertension and cardiac valvulopathy by drugs used in obese patients (fenfluramine/phentermine, benfluorex) or to treat Parkinson's disease (pergolide), raised a question about the cardiovascular risk of compounds targeting some serotonergic receptors. Interestingly, valve lesions induced by these compounds are similar to those observed in the carcinoid heart-cardiac remodeling caused by tumors secreting high amounts of 5-HT. On the other hand, some epidemiologic data have suggested that serotonergic blockers, such as second-generation antipsychotics, may protect the cardiovascular system in schizophrenia. Finally, a link between depression, the use of serotonin selective reuptake inhibitor antidepressants and cardiovascular risk was suggested many years ago.

The aim of this short review is to highlight the contribution of 5-HT and its receptors to cardiovascular tissue remodeling, with a particular emphasis on cardiac hypertrophy, fibrosis and valve degeneration. Some new aspects of serotonergic receptors in blood pressure control will also be discussed. A brief description of the peripheral serotonergic system will be given initially. The deleterious cardiovascular effects of 5-HT and serotonergic agonists are summarized in Fig. 1.

Serotonin synthesis, metabolism and effectors

Most (90%) of the 5-HT synthesized in the body comes from the periphery, where it is mainly produced by gut enterochromaffin cells from the essential amino acid, tryptophan, and the limiting enzyme, tryptophan hydroxylase-1; it is then taken up by the serotonin transporter (SERT) in platelets, and stored in dense granula together with calcium and adenosine triphosphate. When released by platelets, 5-HT triggers biological effects through its interaction with membrane receptors; it can also act through intracellular mechanisms involving oxidative stress generation, following its metabolism by mitochondrial monoamine oxidase A (MAO-A) and putative protein serotonylation by transglutaminase-2. The main 5-HT metabolite generated by MAO-A is 5-hydroxyindole acetic acid (5-HIAA). Fifteen 5-HT receptors belonging to seven families have now been identified. The 5-HT_3-ionotropic receptor is a pentameric cationic channel blocked by molecules of the ''setron'' family. Other receptors are G-protein coupled: Gi-mediated negative regulation of adenylyl cyclase for 5-HT_1 and 5-HT_5; Gs-mediated activation of adenylyl cyclase for 5-HT_4, 5-HT_6 and 5-HT_7; and Gq-mediated stimulation of phospholipase C

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