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## **Serotonin in the heart: the beauty and the beast**

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# ACTA PHYSIOLOGICA

## Serotonin in the heart: the beauty and the beast

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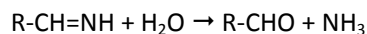
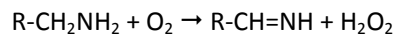
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Review

### ***Serotonin in the heart: the beauty and the beast***

Existence of a cross-talk between administration of antidepressants targeting serotonin re-uptake and its degradation and heart development in foetus has been acknowledged at a terrible price. The use of selective serotonin reuptake inhibitor (SSRI) paroxetine during the first trimester of pregnancy was associated with an increased risk in development of heart defects and late first trimester spontaneous abortions to which severe heart defects contributed (Sadler, 2011). As the importance of serotonin during myocardial development was recognised, pieces of the puzzle began to assemble on multiple actions of 5-HT in embryonic and adult heart. Many of these pieces are still missing.

From four classes of serotonin receptors, one (5-HT<sub>3</sub> receptors) is comprised of ligand-gated ion channels, whereas the other three (5-HT<sub>1/5</sub>, 5-HT<sub>2</sub> and 5-HT<sub>4/6/7</sub> receptors) are G protein-coupled receptors. 5-HT<sub>2B</sub> and 5-HT<sub>4</sub> receptors are present in the heart. 5-HT<sub>2B</sub> receptors play an important role in cardiac development during embryogenesis, promoting proliferation and differentiation of cardiomyoblasts (Nebigil et al., 2000). In adult heart this receptor is involved in progression of myocardial hypertrophic remodelling (Nebigil and Maroteaux, 2003). 5-HT<sub>4</sub> receptor controls Ca<sup>2+</sup> currents through L-type calcium channels and modulates pacemaker currents in atrial myocytes, and, when hyperactivated, promotes arrhythmia (Gergs et al., 2010). Antagonists of this receptor are tested as antiarrhythmic drugs (Doggrell, 2003). Apart from receptor-mediated 5-HT signalling, hydrogen peroxide produced from serotonin during its degradation inside the cells serves as a second messenger or as a damaging pro-oxidant (Cooper et al., 2003). The underlying reactions catalyzed by monoamine oxidases (MAO) in the mitochondria of multiple cell types including cardiomyocytes (Sivasubramaniam et al., 2003) are:



Although SSRIs show their beastly look in the first trimester of human life, these drugs appear to give the adult heart a helping hand reducing the risk of myocardial infarction (MI) (Sauer et al., 2001). Relief that depressed patients receive after SSRIs administration contributes to an attenuation of incidence of MI. But this is not all these drugs do. Serotonin transporters (SERTs) in platelets are also suppressed by systemic SSRI administration. Platelets are known to take up peripheral serotonin which is mainly synthesised by enterochromaffin cells in the gut and release it upon activation promoting thereby clot formation. Patients on SSRIs have serotonin-depleted platelets that are not capable of facilitating thrombosis (Bismuth-Evenzal et al., 2012). Valve cardiomyocytes are also possessing SERT {Pavone, 2008 #18}. Such a broad range of effects of SSRIs enables these drugs to protect the heart from MI, whereas other classes of equally effective antidepressants do not reduce the risk of MI (Sauer et al., 2001).

Unfortunately, preventive treatment against MI is hardly possible. Could SSRIs also be viewed as attractive candidates for reducing myocardial damage in ischemic or post-MI heart? Do local increases in interstitial 5-HT contribute to ischemic heart damage or ischemia-reperfusion injury?

The study of Sonobe et al (Sonobe et al., 2012) gives us some clues pointing towards active regulation of interstitial serotonin levels in rabbit heart in the course of ischemia-reperfusion *in vivo*. The authors used microdialysis technique to monitor 5-HT levels in the interstitial space within the

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3 ischemic area of rabbit heart. The impact of 5-HT production, reuptake and degradation on the  
4 maintenance of serotonin balance was assessed in healthy heart, during ischemic insult and after the  
5 restoration of coronary blood perfusion. Coronary occlusion was associated with a gradual interstitial  
6 5-HT accumulation. Release of the coronary clamp was followed by an immediate dramatic increase  
7 in serotonin levels which then declined over the 10-70 min of perfusion. Re-uptake of 5-HT actively  
8 counteracted its release during reperfusion. Degradation of 5-HT by MAO occurred both during the  
9 ischemic phase and at reperfusion.  
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12 These findings let one suggest that inhibition of serotonin re-uptake will keep 5-HT<sub>4</sub> and 2a  
13 receptors in cardiomyocytes active promoting most likely positive inotropic effects and sustaining  
14 contractile function (Levy et al., 2008). However, increased re-uptake of 5-HT by cardiomyocytes  
15 along with restoration of oxygen supply of the heart muscle provides more fuel to MAO-A, and  
16 aggravates oxidative stress at reperfusion (Kaludercic et al., 2011). Thus blocking the SERT with SSRI  
17 including fluoxetine as well as suppressing MAO activity during reperfusion may appear to be very  
18 beneficial. This therapeutic approach will potentially reduce the risk of re-occlusion of coronary  
19 vessels as 5-HT stores in platelets will be depleted and reduce oxidative stress in myocardial tissue at  
20 reperfusion rescuing mitochondria from irreversible damage and protecting the tissue from  
21 reperfusion injury (Ong and Gustafsson, 2012). Apart from platelets, vagal afferents, and resident  
22 mast cells cardiomyocytes themselves have been recently shown to express their own 5-HT (Ponické  
23 et al., 2012) and possess their own serotonin re-uptake machinery (Pavone et al., 2008). What is the  
24 impact of this source of 5-HT on the interstitial serotonin pool and if SERT and MAO inhibition  
25 interfere with 5-HT acting in a paracrine and an autocrine fashion remains to be investigated. The  
26 study of Sonobe et al. marks the beginning of a long and fascinating journey at the end of which  
27 knowledge will be transformed into a new treatment strategy. This new strategy will use the strong  
28 sides of SSRIs avoiding the odds of careless interference with vital physiological actions of 5-HT.  
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