



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
Main Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2013

Serotonin in the heart: the beauty and the beast

Bogdanova, A

DOI: <https://doi.org/10.1111/j.1748-1716.2012.02472.x>

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: <https://doi.org/10.5167/uzh-71020>

Originally published at:

Bogdanova, A (2013). Serotonin in the heart: the beauty and the beast. *Acta Physiologica*, 207(2):206-207.

DOI: <https://doi.org/10.1111/j.1748-1716.2012.02472.x>

ACTA PHYSIOLOGICA

Serotonin in the heart: the beauty and the beast

Journal:	<i>Acta Physiologica</i>
Manuscript ID:	APH-2012-07-0162
Manuscript Type:	Editorial
Date Submitted by the Author:	02-Jul-2012
Complete List of Authors:	Bogdanova, Anna; University of Zurich, Institute of Veterinary Physiology;
Key Words:	serotonin, reuptake , heart, ischemia-reperfusion, selective serotonin reuptake inhibitors

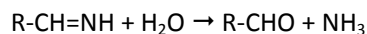
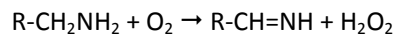
SCHOLARONE™
Manuscripts

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-HT₃ receptors) is comprised of ligand-gated ion channels, whereas the other three (5-HT_{1/5}, 5-HT₂ and 5-HT_{4/6/7} receptors) are G protein-coupled receptors. 5-HT_{2B} and 5-HT₄ receptors are present in the heart. 5-HT_{2B} 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-HT₄ receptor controls Ca²⁺ 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

1
2
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.
10
11

12 These findings let one suggest that inhibition of serotonin re-uptake will keep 5-HT₄ 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 (Ponicke
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.
29
30
31
32
33

34 References

- 35
36 Bismuth-Evenzal, Y., Gonopolsky, Y., Gurwitz, D., Iancu, I., Weizman, A. & Rehavi, M. 2012. Decreased
37 serotonin content and reduced agonist-induced aggregation in platelets of patients
38 chronically medicated with SSRI drugs. *J Affect Disord*, **136**, 99-103.
39 Cooper, J., Bloom, F. & Roth, R. 2003. Serotonin (5-hydroxytryptamine), histamine and adenosine.)
40 *The Biochemical Basis of Neuropharmacology*. Oxford University Press, New York.
41 Doggrel, S. A. 2003. The role of 5-HT on the cardiovascular and renal systems and the clinical
42 potential of 5-HT modulation. *Expert Opin Investig Drugs*, **12**, 805-23.
43 Gergs, U., Baumann, M., Bockler, A., Buchwalow, I. B., Ebel, H., Fabritz, L., Hauptmann, S., Keller, N.,
44 Kirchhof, P., Klockner, U., Ponicke, K., Rueckschloss, U., Schmitz, W., Werner, F. & Neumann,
45 J. 2010. Cardiac overexpression of the human 5-HT₄ receptor in mice. *Am J Physiol Heart Circ*
46 *Physiol*, **299**, H788-98.
47 Kaludercic, N., Carpi, A., Menabo, R., Di Lisa, F. & Paolucci, N. 2011. Monoamine oxidases (MAO) in
48 the pathogenesis of heart failure and ischemia/reperfusion injury. *Biochim Biophys Acta*,
49 **1813**, 1323-32.
50 Levy, F. O., Qvigstad, E., Krobert, K. A., Skomedal, T. & Osnes, J. B. 2008. Effects of serotonin in failing
51 cardiac ventricle: signalling mechanisms and potential therapeutic implications.
52 *Neuropharmacology*, **55**, 1066-71.
53 Nebigil, C. G., Choi, D. S., Dierich, A., Hickel, P., Le Meur, M., Messaddeq, N., Launay, J. M. &
54 Maroteaux, L. 2000. Serotonin 2B receptor is required for heart development. *Proc Natl Acad*
55 *Sci U S A*, **97**, 9508-13.
56
57
58
59
60

- 1
2
3 Nebigil, C. G. & Maroteaux, L. 2003. Functional consequence of serotonin/5-HT_{2B} receptor signaling
4 in heart: role of mitochondria in transition between hypertrophy and heart failure?
5 *Circulation*, **108**, 902-8.
- 6 Ong, S. B. & Gustafsson, A. B. 2012. New roles for mitochondria in cell death in the reperfused
7 myocardium. *Cardiovasc Res*, **94**, 190-6.
- 8 Pavone, L. M., Spina, A., Lo Muto, R., Santoro, D., Mastellone, V. & Avallone, L. 2008. Heart valve
9 cardiomyocytes of mouse embryos express the serotonin transporter SERT. *Biochem Biophys*
10 *Res Commun*, **377**, 419-22.
- 11 Ponicke, K., Gergs, U., Buchwalow, I. B., Hauptmann, S. & Neumann, J. 2012. On the presence of
12 serotonin in mammalian cardiomyocytes. *Mol Cell Biochem*, **365**, 301-12.
- 13 Sadler, T. W. 2011. Selective serotonin reuptake inhibitors (SSRIs) and heart defects: potential
14 mechanisms for the observed associations. *Reprod Toxicol*, **32**, 484-9.
- 15 Sauer, W. H., Berlin, J. A. & Kimmel, S. E. 2001. Selective serotonin reuptake inhibitors and
16 myocardial infarction. *Circulation*, **104**, 1894-8.
- 17 Sivasubramaniam, S. D., Finch, C. C., Rodriguez, M. J., Mahy, N. & Billett, E. E. 2003. A comparative
18 study of the expression of monoamine oxidase-A and -B mRNA and protein in non-CNS
19 human tissues. *Cell Tissue Res*, **313**, 291-300.
- 20 Sonobe, T., Akiyama, T., Du C-K., Zhan, D.-Y. & Shirai, M. 2012. Contribution of serotonin uptake and
21 degradation to myocardial interstitial serotonin levels during ischemia-reperfusion in rabbits.
22 *Acta Physiol in press*.
- 23
24
25
26
27

28 Anna Bogdanova

29 Institute of Veterinary Physiology, Vetsuisse Faculty and the Zurich Center for Integrative Human
30 Physiology, University of Zurich, Zurich, Switzerland

31 E-mail: annab@access.uzh.ch
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60