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Letter to the Editor

High-dose oral intake of serotonin induces valvular heart disease in rabbits

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Carcinoid tumors are rare neuroendocrine malignancies, often originating from enterochromaffin cells in the gastrointestinal tract. They can secrete serotonin (5-hydroxytryptamine, 5-HT), which is largely inactivated by the liver [1]. Carcinoid heart disease occurs when tumor cells metastasize to the liver, as the vasoactive substances produced are able to reach the systemic circulation via the hepatic vein, causing deposition of fibrous tissue on the endocardial surfaces of the heart [2]. It is predominantly manifested by right-sided valvular heart disease (VHD). Scavenging enzymes in the pulmonary endothelium may explain why left-sided cardiac involvement is unusual [3]. The severity of cardiac damage is correlated with the plasmatic levels of serotonin, but the low specificity of serotonin for cardiac damage suggests that serotonin may be necessary but not sufficient to induce cardiac lesions [4]. Therefore, other factors combined with serotonin might be required to induce VHD. However, recent animal studies confirmed the development of carcinoid-like valvular deposits in rats after 3 months of daily subcutaneous/intraperitoneal serotonin injections to avoid the liver first-pass clearance [5,6]. Whether oral administration of serotonin can also induce VHD is unknown. We hypothesized that long-term oral serotonin overload in rabbits can lead to VHD, mimicking serotonin-induced lesions of carcinoid heart disease.

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Ten New Zealand White rabbits (2–2.5 kg) were used to assess serotonin cardiac toxicity and pharmacokinetics. Five rabbits received placebo and five others 80 mg/kg of serotonin via drinking water for 16 weeks. Levels of circulating serotonin (5-HT) and its conversion to 5-hydroxyindoleacetic acid (5-HIAA) were determined in platelet poor plasma and urine samples (daily for 3 days post-administration and at 10 days). Doppler echocardiographic examinations (parasternal and apical views) (Vivid 9 Pro system, GE Medical Systems, Milwaukee, WI, USA) were performed at baseline and at 16 weeks, followed by necropsy and histological examination of the heart. The study protocol was performed in agreement with the European Convention for the Protection of Animals Used for Experimental and Other Scientific Purposes and after approval by the Ethics Committee of the University of Liège, Belgium.

A sustained increase in blood serotonin levels and of its urine metabolite was observed in serotonin treated animals (Table 1). At sacrifice, body weight was not significantly different between groups (Table 1). Each valve was assessable in all animals during the echocardiographic study (Table 2). There was no valvular abnormality at baseline. All serotonin treated rabbits developed moderate ($n = 1$) to severe ($n = 4$) tricuspid regurgitation while three rabbits of the placebo group had trivial tricuspid regurgitation at 16 weeks. Mean transtricuspid pressure gradient was 13.6 ± 2.7 mm Hg. Two animals had mild aortic regurgitation and one had severe regurgitation. Three had mild mitral regurgitation and one had moderate regurgitation. Pulmonary regurgitation was present in three serotonin treated rabbits (Fig. 1). None of the placebo rabbits displayed aortic, mitral or pulmonary regurgitation. No rabbit had echocardiographic signs of restrictive leaflet motion. Histological examination revealed thickened aortic, mitral, and tricuspid leaflets in the serotonin group (measured on the digital microscopic images) (Table 1). Valvular thickening was due to diffuse myxoid change in the sponge layer of the leaflets. Several areas of chondroid metaplasia were noted in the serotonin treated rabbits. A few carcinoid-like plaques characterized by a collection of myofibroblasts within an extracellular matrix of collagen ground substance were also present in these rabbits (Fig. 2). Valvular fibrosis with dense collagen was not observed. Macroscopically, left ventricular cavities seemed more dilated in the serotonin group (not shown).

In the present study, we have demonstrated, for the first time that high dose long-term oral administration of serotonin can lead to VHD in rabbits. The tricuspid valve was commonly affected with moderate-

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Table 1
Effects of oral administration of serotonin on rabbit body weights and heart valve thicknesses. Levels of circulating serotonin and urine metabolite at steady state.

	Plasma serotonin (μM)	Urine 5-HIAA (mg/l)	Body weight (kg)		Heart weight (g)	AV thickness (μm)	MV thickness (μm)	TV thickness (μm)
	10 days	10 days	day 0	16 weeks	16 weeks	16 weeks	16 weeks	16 weeks
Non-treated (n = 5)	0.22 ± 0.21	19.17 ± 4.91	2 ± 0.05	3.7 ± 0.24	8.0 ± 0.95	110 ± 59	128 ± 90	96 ± 70
Serotonin (n = 5)	0.58 ± 0.34*	181.7 ± 33.07**	2.16 ± 0.19	4.24 ± 0.38	8.97 ± 0.85	149 ± 94***	187 ± 128***	134 ± 85***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs. non-treated (t-test).
5-HIAA = 5-hydroxyindoleacetic acid, AV = aortic valve, MV = mitral valve, TV = tricuspid valve.

Table 2
Summary of color Doppler echocardiographic valvular regurgitation (number of rabbit per category) at 16 weeks follow-up.

	Tricuspid regurgitation	Aortic regurgitation	Mitral regurgitation	Pulmonary regurgitation
Non-treated (n = 5)				
Trivial	3	0	0	0
Mild	0	0	0	0
Moderate	0	0	0	0
Severe	0	0	0	0
Serotonin (n = 5)				
Trivial	0	0	0	0
Mild	0	2	3	1
Moderate	1	0	1	2
Severe	4	1	0	0

to-severe regurgitation in all serotonin treated rabbits. The left-sided valves were less frequently and severely involved in the disease process. No serotonin treated rabbits had echocardiographic signs of restrictive valvulopathy or dense collagen deposits at histology. In diseased valves, histological examination, however, confirmed the carcinoid-like heart disease with carcinoid-like plaque, thickened valve (increased spongiosa), and chondroid metaplasia. Our study confirmed that serotonin is most likely involved in the pathogenesis of carcinoid heart disease [5,6]. In fact, when the liver metabolic activity is exhausted, VHD can develop in the presence of sustained high circulating levels of serotonin [7]. The activation of the 5-HT(2B) serotonin receptors in the heart valves has been suggested as the main mechanism associated with carcinoid heart disease and drug-induced VHD [8,9]. When stimulated, they would promote mitogenic pathways and activate production of glycosaminoglycan and collagen via upregulation of transforming growth factor-β1 (TGF-β1) [10]. Whether serotonin receptor antagonists can prevent cardiac changes resulting from hyperserotonemia needs to be examined. However, although the 5-HT(2B)R/TGF-β1 axis seems to represent a common pathophysiological pathway, a variability of individual susceptibility to develop VHD lesion has been described. For instance, some carcinoid patients with high circulating serotonin levels do not develop heart disease. Lower 5-HT(2B) receptor responsiveness to serotonin, higher metabolic rate, genetic or epigenetic determinants or other protective mechanisms could play a role. The involvement of 5-HT(2B) receptor activation in the development of VHD is thus an important topic of investigation. Further studies should focus on the molecular mechanisms and factors associated with serotonin-induced VHD.

Conflict of interest

None.

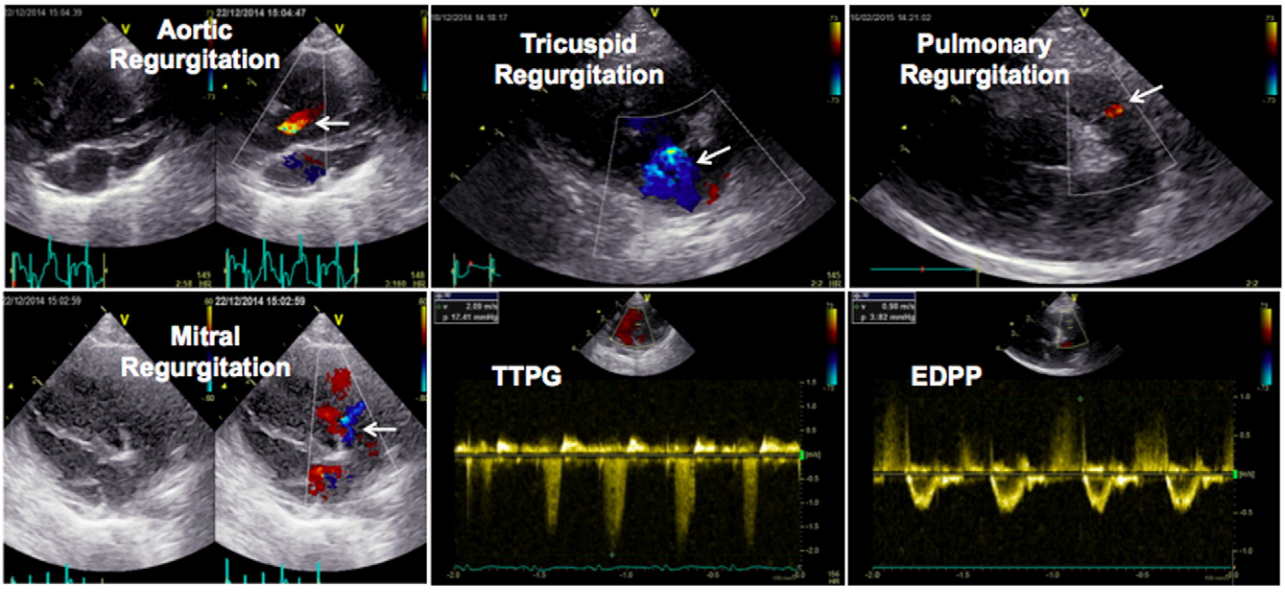

Fig. 1. Examples of valvular regurgitation in serotonin treated rabbits: severe aortic regurgitation, severe tricuspid regurgitation, moderate mitral regurgitation, mild pulmonary regurgitation (arrows). TTPG: transtricuspid pressure gradient derived from the velocity of the tricuspid regurgitation jet; EDPP: end-diastolic pulmonary pressure derived from the velocity of the pulmonary regurgitation jet. Both TTPG and EDPP are elevated demonstrating the presence of pulmonary hypertension.