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CORRESPONDENCE

Pulmonary hypertension, left ventricular dysfunction and plasma serotonin: commentary on Deuchar *et al.*

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We read with great interest the research article by Deuchar *et al*. (2002). With respect to this, we would like to discuss those experimental data including the demonstrated role played by plasma serotonin (f-5HT) in both pulmonary vasoconstriction and bronchial constriction.

Hervé *et al*. (1995) demonstrated the close association between f-5HT and pulmonary hypertension. Belohlavkova *et al*. (2001) demonstrated that the serotonin releasing agent fenfluramine triggered pulmonary vasoconstriction. Lechin *et al*., in an open study, were able to provoke dramatic improvement of 13 severe pulmonary hypertension patients with relatively low doses of tianeptine, a drug which enhances platelet serotonin uptake and reduces f-5HT sharply (Lechin & van der Dijs, 2002; Lechin *et al*., 2002). Conversely, we found that drugs which increase f-5HT like buspirone and serotonin uptake inhibitors worsened pulmonary hypertension and bronchial asthma patients (Lechin, 2000; Lechin *et al*., 1998c).

Circulating serotonin includes platelet-serotonin = 95–98% and plasma serotonin or f-5HT = 2–5%. F-5HT increases because of platelet-aggregation (secondary to plasma epinephrine rises) (Larsson *et al*., 1989) and during excessive parasympathetic activity (Lechin, 2000). Two factors converge to provoke the latter: (1) parasympathetic nerves excite the enterochromaffin cells, the almost only source of blood serotonin (Tobe *et al*., 1976); and (2) circulating acetylcholine interferes with the uptake of plasma serotonin by platelets (Rausch *et al*., 1985).

The fraction of intestinal serotonin released to the blood stream is cleared by the liver and lungs (Kjellstrom *et al*., 1982). With respect to the latter, it has been definitively demonstrated that f-5HT raises during asthma attacks (Lechin *et al*., 1996) and during worsening of pulmonary hypertension patients, both of which syndromes are dramatically improved by tianeptine (Lechin *et al*., 1998a,b, 2002). According to all the above, we suggest that all the *in vivo* studies addressed to investigate pulmonary vasoconstriction, should include assessment of f-5HT which in our opinion is the most important protagonist playing a role in this disorder.

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Reply to Lechin *et al.*

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We thank Dr. Lechin for his commentary on plasma serotonin (5-HT) and pulmonary hypertension (PHT). We are very aware of the literature concerning plasma 5-HT and the association of plasma 5-HT with PHT and, indeed MacLean *et al.* have reviewed this area recently (see MacLean, *TIPS*, 20, 471–509, 1999; MacLean *et al.*, *Br. J. Pharmacol.*, 131, 161–168, 2000).

Despite this there is actually more recent evidence that suggests that it is not so much the rise in plasma 5-HT that promotes PHT but the increase in its transport into the pulmonary vascular smooth muscle cells (see Eddahibi *et al.*, *J. Clin. Invest.*, 108, 1141–1150, 2001). Indeed, 5-HT transporter inhibitors reduce experimental PHT (Eddahibi *et al.*, *Am. J. Resp. Crit. Care Med.*, 165, A748, 2002), and are being considered for clinical trials in PPH. As your own work demonstrates, a rise in plasma 5-HT alone is not sufficient for the development of PHT. Future research will certainly need to clarify the relationship between the serotonin transporter and plasma 5-HT. In addition, it is widely felt that the literature pertaining to plasma 5-HT levels is misleading. Reported levels are much higher than physiologically normal 5-HT levels due to platelet contamination. This is due to the concentration gradient between plasma and platelets. Plasma free 5-HT is normally extremely low, around 0.7 nmol L^{-1}, when measured accurately (Beck *et al.*, *Biochem. Biophys. Res. Comm.*, 196, 260–266, 1993); whilst platelet levels are well over 100 fold higher (Maurer-Spurej *et al.*, *Br. J. Haematol.*, 116, 604–611, 2002). Hence, even slight disruption of the platelets causes erroneous results. It should be advised that urine HIAA excretion be measured as well as plasma 5-HT levels. We do, however, acknowledge that the role of free plasma 5-HT is an interesting area requiring further consideration.