Arginine-induced pancreatitis: involvement of the autonomic nervous system?

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TO THE EDITOR: Dawra et al. (1) were able to trigger acute pancreatitis in mice after the administration of L-arginine. In addition, acute inflammation in the pancreas was associated with lung injury. With respect to this, we would like to offer some insight into the possible physiological, pathophysiological, neuroautonomic, and neuropharmacological mechanisms underlying pancreatitis and pancreatobiliary drainage plus the possible role played by arginine.

In 1992 we published two clinical reports dealing with the dramatic improvement of patients affected by acute pancreatitis treated with intramuscularly injected clonidine (0.15 mg each 12 h) (7, 8). Normalization of all plasma and clinical parameters was obtained with this therapy. All clinical symptoms disappeared abruptly. Absolute normalization of all pancreatic enzymes paralleled clinical improvement. Normalization of the raised plasma catecholamines, indolamines (serotonin), and cortisol were also registered, after the first clonidine injection. The above preliminary results have been further ratified and published by us and others (10, 16, 21). We have successfully treated 73 acute pancreatitis patients throughout the last 15 years (without side effects) (9).

The pancreatic inflammation triggered by L-arginine reported by Dawra et al. (1) might be attributed to the fact that a small oral dose of this amino acid (50 mg) is able to provoke significant changes of plasma neurotransmitters. With respect to this, we demonstrated that 50 mg of oral L-arginine provoked significant rise of plasma norepinephrine (NE), dopamine (DA), and free serotonin in the plasma (f-5HT). On the contrary, plasma epinephrine (Ep) was reduced by the drug. In addition, despite the fact that the NE-to-Ep plasma ratio was enhanced by the drug, the NE-to-DA ratio was reduced (2). Our long experience dealing with the assessment of circulating neurotransmitters throughout the last 30 years allowed us to conclude that L-arginine provoked an enhancement of neural sympathetic activity (NE-to-DA ratio) plus an increase of parasympathetic activity. This latter was demonstrated by the increase of f-5HT. This parameter reflects the level of circulating acetylcholine (ACh), which interferes with platelet uptake of serotonin (12, 18). The fact that no platelet aggregation was detected in the subjects included in our research study discarded this factor, which is also able to enhance f-5HT (12). The enhancement of parasympathetic activity reported in subjects taking L-arginine is consistent with both the heart rate and the diastolic blood pressure decreases registered in them. However, the fact that diastolic but not systolic blood pressure decreased despite the rise of plasma NE might be associated to the well-known fact that there exists a dopaminergic pool at the end of the sympathetic nerves. This dopamine is released during sympathetic excitation and modulates the secondary release of NE. In addition, these sympathetic terminals are crowded with DA-2 inhibitory autoreceptors whose stimulation avoids excessive NE release from them. However, predominance of the DA release triggers diastolic blood pressure reduction, as reported in several studies (4–6, 14, 20).

Summarizing our results, we concluded that L-arginine was able to provoke enhancement of both parasympathetic and neural sympathetic activity plus a reduction of adrenal sympathetic drive. According to the above, we believe that the arginine-induced pancreatitis, reported by Dawra et al. (1), may be associated to the parasympathetic hypersecretion of pancreatic juice, which could not be drained through the pancreatic ducts because of the well-known contractile effect exerted by the sympathetic nerves that release NE at this level (19). This overwhelming acinar over ductular predominance constitutes the main pathophysiological mechanism responsible for pancreatitis, pancreatic cysts and cystic fibrosis (11). We also demonstrated that not only pancreatic but biliary drainage should be taken into account to understand the pathophysiology of pancreatitis. The pancreatic and biliary ducts share a common ductular drainage at the choledocus and the sphincter of Oddi (3, 15, 17). With respect to this, we demonstrated that both neural sympathetic activity (NE) and circulating serotonin modulate biliary motility (10, 13, 15). These neurotransmitters play a primordial role in the gallbladder and the sphincter of Oddi motility; thus any discussion dealing with the pancreatobiliary pathophysiology might be carried out as a whole.

REFERENCES