Is there a therapeutic role for Agmatine?

Agmatin`in terapötik rolü var mı?

Agmatine is an endogenous polycationic amine synthesized from L-arginine by arginine decarboxylase. It is present in plasma and widely distributed in mammalian tissues (1,2). Agmatine binds and activates both α_2-adrenegic receptors and I_1- and I_2- imidazoline receptors (3). It also blocks the ligand-gated N-methyl-D-aspartate (NMDA) receptor channel in neuronal tissue (3). Though activation of imidazoline receptors, agmatine inhibits catecholamine release from chromaffin cells and stimulates insulin release from pancreatic β-cells (4,5). It also inhibits proliferation of both rat and human vascular smooth muscle cells via I_2- imidazoline receptors (6,7).

Since agmatine actives α_2-adrenergic receptors, it can facilitate the release of norepinephrine from sympathetic nerve terminals. In the current issue of this journal, agmatine was shown to increase contractile force of the isolated frog heart in response to high-frequency (16 Hz) electrical stimulation (8). The high-frequency stimulation presumably activated local sympathetic nerve terminals within the myocardium to release catecholamines. The increase in contractility in response to high-frequency stimulation was blocked by yohimbine, an α2-adrenergic blocker, but not by the imidazoline blocker, idazoxan. Furthermore, agmatine had no effect on the ability of exogenous norepinephrine to increase contractile force, indicating the absence of an effect of agmatine on post-junctional adrenergic receptors. These results suggest that the agmatine may act as a positive inotrope in the frog heart by enhancing the release of catecholamines from sympathetic nerve terminals. However, it must be recognized that the administration of agmatine in vivo may have effects that are quite different from its effects in vitro. The intravenous administration of agmatine to normal and salt-sensitive hypertensive rats has been shown to produce a dose-dependent reduction in heart rate and contractility that was mediated mainly by I_1-imidazoline receptors (9). Thus, the effect of agmatine to increase cardiac contractility by facilitation of the sympathetic neurotransmission might be offset in the intact animal by a central effect of agmatine to reduce cardiac sympathetic efferent tone.

Agmatine also exerts biological effects that are independent of its binding to α2-adrenergic or imidazoline receptors. Agmatine has been shown to inhibit voltage-gated calcium channels to reduce the influx of calcium in both cardiac and neuronal tissue (10,11). In addition, agmatine is a competitive inhibitor of all isoforms of nitric oxide synthase (NOS) and may protect against the excess production of nitric oxide when inflammation leads to an increase in NOS activity (12). Agmatine prevented the decrease in blood pressure and renal function normally associated with sepsis in rats given endotoxin, and increased survival of endotoxin-treated mice (13). It was also shown to reduce infarct size in a mouse model of transient focal cerebral ischemia and protect cultured neurons from ischemic-like injury (14). Furthermore, agmatine exerted a protective effect against ischemia-reperfusion injury in the isolated rat heart (15). In a rat model of mesangial proliferative glomerulonephritis, agmatine reduced mesangial cell proliferation through inhibition of ornithine decarboxylase, the rate-limiting enzyme in polyamine biosynthesis (16).

Since agmatine is a relatively nontoxic compound that has a wide spectrum of biological activity, it may well have therapeutic value in the treatment of various diseases including cardiovascular disease. Although the experimental studies on the exogenous administration of agmatine appear promising, the literature available to date is not sufficient to establish a definitive therapeutic role for agmatine. Additional studies are needed to determine if agmatine has a therapeutic role in the in the treatment of human diseases.

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