Physiological Importance of ATP Released From Nerve Terminals and Its Degradation to Adenosine in Humans

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The paper by Taddei et al. in this issue of Circulation deals with two important physiological aspects of endogenous purine compounds, both of which have been controversial for quite some time. The first is the release of ATP from nerve terminals and the second, the antiadrenergic action of adenosine. In their study in humans, Taddei et al found evidence suggesting a) reflex vasoconstriction mediated in part by ATP and b) the modulation of this reflex by adenosine, a product of enzymatic degradation of ATP. The latter could be a manifestation of the antiadrenergic action of endogenous adenosine under experimental conditions that closely resemble physiological ones.1 Thus, these observations demonstrate for the first time in humans that the release of ATP, its degradation to adenosine, and the inhibition of neurotransmitter release by adenosine constitute an important physiological regulatory feedback loop.

The idea that some nerves release more than one transmitter was originally proposed by Burnstock2 in what has been termed the cotransmitter hypothesis.

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Since then, extensive evidence for sympathetic cotransmission of ATP and norepinephrine (NE) has been obtained in several studies, including those by Westfall and colleagues3 on the isolated guinea pig vas deferens, Langer and Pinto4 on the cat nictitating membrane, and Su5 on a number of different blood vessels from various animals. Numerous studies have indicated that ATP, released as a cotransmitter with NE, is responsible for the adrenoceptor-independent component of sympathetic vasoconstriction.6 Supporting evidence includes release of ATP during nerve stimulation; similarity between the effect of ATP and prazosin-resistant responses to sympathetic nerve stimulation; antagonism of prazosin-resistant neurotransmission by the selective P2x-purinoceptor antagonist ary lazidoaminopropionyl-ATP; and selective desensitization of the P2-purinoceptor by prolonged exposure to α,β-methylene ATP (α,β-meATP). In addition, destruction of sympathetic nerve terminals with 6-hydroxydopamine abolishes the purinergic as well as noradrenergic responses, indicating that both ATP and NE are coreleased from sympathetic nerves.

There is considerable variation in the proportions of ATP and NE utilized in perivascular sympathetic nerves. For example, a substantial ATP component is involved in sympathetic neurotransmission in the rabbit saphenous artery.7 Thus, prazosin reduces the response of this vessel to sympathetic nerve stimulation by less than 30% even at high stimulation frequencies, which favor the NE response, and the remainder is blocked by α,β-meATP. Furthermore, following reserpine treatment, which depletes NE from sympathetic nerves, prazosin has no effect, but the entire response is abolished by α,β-meATP.8 In addition, in mesenteric9 and hepatic10 arteries the ATP contribution to sympathetic cotransmission is also high. In the rabbit jejunal artery, ATP seems to be the sole mediator of the contractile response to sympathetic nerve stimulation, and NE acts as a presynaptic modulator.11 In contrast, the ATP involvement appears to be smaller relative to that of NE in the sympathetic nerves supplying the rat tail artery and rabbit ear artery.6 Indeed, in the rat tail artery, the prazosin-resistant (i.e., purinergic) mechanical response to perivascular nerve stimulation was observed only with short bursts of pulses lasting about a second, which appear to favor the ATP component.12 This might mean that NE is the more important component of sympathetic cotransmission during activities such as mild exercise, and ATP is the more important during stress, when short burst frequencies occur in sympathetic nerves.13

Evidence for adrenergic-purinergic cotransmission has been obtained both in vivo and in vitro. For example, skeletal muscle vasodilation produced by hypothalamic stimulation in anaesthetized rabbits seems to be mediated by ATP released from sympathetic nerves.14 More recently, a contribution of ATP
to sympathetic vasopressor responses of the pithed rat has also been demonstrated.\textsuperscript{15,16} The latter responses, but not the $\alpha$-adrenoceptor-mediated responses, were blocked by nifedipine. In isolated rat kidney, renal vasoconstriction elicited by periartrial nerve stimulation was mainly due to release of a purinergic transmitter, probably ATP, and due to a lesser extent to release of NE.\textsuperscript{17} Studies of autoperfused cat intestinal circulation have shown that the initial rapid phase or prazosin-resistant vasoconstriction is completely abolished after desensitization of the $P_{2\alpha}$-purinoceptor with $\alpha,\beta$-meATP.\textsuperscript{18} Stimulation of the lumbar sympathetic nerves in the ganglion-blocked rabbit constricts the hindlimb vasculature independent of $\alpha$-adrenoceptor activation.\textsuperscript{19} Finally, the reflex increase in sympathetic tone in cutaneous veins upon exposure to cold is resistant to adrenoceptor antagonists, but is inhibited by desensitization of the $P_{2\gamma}$-purinoceptor with $\alpha,\beta$-meATP.\textsuperscript{20}

The relative importance of NE and ATP as mediators of sympathetic neural control of blood vessels changes during development.\textsuperscript{21} There is also some evidence that the ATP component in sympathetic neurotransmission may increase under pathological conditions. For example, ATP seems to have a much greater role in sympathetic cotransmission in spontaneously hypertensive rats compared with that in normotensive rats.\textsuperscript{22}

Based on the findings of the above-mentioned studies it can be concluded that, at least in several species and tissues, ATP is coreleased with NE from perivascular sympathetic nerve terminals and that certain actions of the nucleotide are mediated by a specific $P_{2\gamma}$-purinoceptor. Further studies are required before the physiological role of ATP in this setting is fully elucidated; the data of Taddei et al\textsuperscript{1} are helpful in this respect.

In a study using anesthetized cats,\textsuperscript{23} exogenous adenosine inhibited equally, in a dose-dependent manner, the vasoconstriction of the superior mesenteric artery induced by either nerve stimulation or norepinephrine infusion. However, the adenosine antagonist 8-phenyltheophylline did not alter the vasoconstriction induced by either nerve stimulation or norepinephrine. The discrepancy between the data obtained in this study in animals and the study by Taddei et al\textsuperscript{1} in humans is not readily explained. Species variability and/or the difference in the specific blood vessel studied might account for this discrepancy. These possible explanations notwithstanding, the contradictory results underscore the limitation of the present study,\textsuperscript{1} specifically, that the present evidence for the release of ATP from sympathetic nerve terminals and its degradation to adenosine in humans is indirect.

The study by Taddei et al\textsuperscript{1} emphasizes the actions of adenosine, the product of the rapid degradation of ATP by ectoenzymes; in particular, the antiadrenergic action of the nucleoside is examined. This action of adenosine is both prejunctional and postjunctional: The prejunctional action is the inhibition of neurotransmitter release from nerve terminals, and the postjunctional action is the attenuation of the effects of catecholamines in target cells. Modulation of autonomic neurotransmission by adenosine nucleosides and nucleotides, and the inhibition of NE release from sympathetic nerve terminals in particular, has been shown in various tissues of several animal species.\textsuperscript{24} Several mechanisms for the decrease in neurotransmitter release caused by adenosine have been proposed, including alterations in $Ca^{2+}$ influx and/or impairment of $Ca^{2+}$-dependent processes in nerve terminals.\textsuperscript{25,26} Although the postreceptor reaction cascade is not fully known, it seems that this action of adenosine is mediated by $A_1$ subtype receptors.\textsuperscript{26}

With regard to the postjunctional action, adenosine inhibits in a dose-dependent manner the positive inotropic effect caused by $\beta$-adrenoceptor stimulation in both isolated guinea pig left atria and perfused hearts.\textsuperscript{27} In addition, adenosine effectively inhibits the metabolic effects of isoproterenol, including the rise in myocardial cyclic AMP. These actions of adenosine were inhibited by theophylline, suggesting mediation by cell surface adenosine receptors.\textsuperscript{28} Based on these findings, it was hypothesized that inhibition of inotropic and metabolic effects of catecholamines could be an important physiological function of endogenous adenosine. These early observations have been confirmed by numerous studies in vitro that have also indicated that the electrophysiological effects of catecholamines are inhibited by adenosine.\textsuperscript{28,29} The mechanism of the antiadrenergic postjunctional action of adenosine is not fully known; however, the following have been established: a) the involvement of the adenylate cyclase–cyclic AMP system, which is explained by the dual coupling of adenylate cyclase to adenosine and catecholamine receptors;\textsuperscript{30} b) adenosine may decrease the affinity of $\beta$-adrenoceptors for catecholamine;\textsuperscript{31,32} and c) the involvement of $A_1$-subtype adenosine receptors.\textsuperscript{33}

The determination of the physiological roles of the antiadrenergic prejunctional and postjunctional actions of adenosine has centered on two major questions. First, can adenosine (endogenous or exogenous) antagonize the effects of catecholamines in vivo? Second, what are threshold levels of adenosine for these actions? With respect to the first question, early studies failed to demonstrate an antiadrenergic postjunctional action of adenosine in vivo;\textsuperscript{34–36} however, more recent studies have shown that specific effects of catecholamines in vivo are significantly inhibited by adenosine. For example, in a preliminary report,\textsuperscript{37} the isoproterenol-enhanced myocardial contractility was attenuated by the potent analog of adenosine, phenylisopropyladenosine (PIA) in anesthetized rats; this effect of PIA was partially reversed by theophylline. In another preliminary report,\textsuperscript{38} the effects of intracoronal isoproterenol on left ventricular excitability were attenuated by adenosine in the anesthetized dog. Similarly, in patients with complete AV block, adenosine markedly attenuated the accel-
eration of the ventricular escape rhythm caused by isoproterenol and aminophylline completely abolished this antiadrenergic effect of adenosine.\textsuperscript{39} Based on these observations and the fact that relatively large amounts of ATP can be released into the extracellular space where it is rapidly degraded by ectoenzymes to adenosine, it can be hypothesized that an antiadrenergic action of ATP is mediated by adenosine.

With regard to the question of threshold levels, it has been suggested that even under physiological conditions adenosine can modulate the sympathetic neural control of the cardiovascular system. For example, it has been hypothesized that with increased to levels high enough to exert an antiadrenergic effect.\textsuperscript{20} However, it is still to be determined whether the adenosine, released under physiological conditions associated with an altered $O_2$ supply/$O_2$ demand ratio, significantly attenuates sympathetic effects in the heart. Viewing adenosine as a cardio-protective endogenous metabolite, it is more tempting to speculate that the antiadrenergic actions of adenosine become significant during pathophysiological conditions when oxygen supply does not meet oxygen demand. The study by Taddei et al\textsuperscript{1} suggests that adenosine originating from degradation of ATP, probably released as a cotransmitter from sympathetic nerves, can exert an antiadrenergic prejunctional action of physiological importance in humans.

References


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