Editorial

Adenosine as an important mediator of post-ischaemic neuronal stunning

John Pernow*
Department of Cardiology, Karolinska Hospital, S-171 76 Stockholm, Sweden
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A brief period of ischaemia is known to induce a prolonged period of reversible myocardial dysfunction despite normalized electrocardiogram and absence of histological signs of necrosis. This was first described by Heyndrickx and co-workers [1] who found that myocardial function was depressed for several hours following a 15-min period of coronary artery occlusion in dogs. Braunwald and Klener [2] subsequently named this phenomenon ‘myocardial stunning’. Although the exact mechanism underlying myocardial stunning is not fully understood, results from several studies indicate that it can be mediated by increased myocyte calcium levels and oxygen-derived free radicals during ischaemia and the initial part of reperfusion [3–5].

In addition to the reduced myocardial contractility, there is also evidence of a long-lasting impairment of neurotransmission in the post-ischaemic heart, a phenomenon known as ‘neuronal stunning’. Martins et al. [6] demonstrated that myocardial contractile function induced by sympathetic nerve stimulation was depressed in ischaemic myocardium. It was later described that the myocardial segment shortening evoked by sympathetic nerve stimulation in dogs was markedly reduced following coronary artery occlusion [7,8]. On the other hand, the response to administration of exogenous noradrenaline was unaffected by ischaemia, which indicates that the sympathetic neurotransmission but not the post-junctional response to noradrenaline was impaired. Neuronal stunning affects not only myocardial contractile function but also regulation of the coronary vasculature. The increase in coronary vascular resistance evoked by sympathetic nerve stimulation is markedly attenuated following coronary artery occlusion whereas the response to exogenous noradrenaline is unaffected [9].

What is the mechanism behind neuronal stunning? It was initially suggested by Miyazaki and Zipes [8] that high potassium, low pH and adenosine each could inhibit sympathetic and vagal neurotransmission and contribute to post-ischaemic neuronal dysfunction. It was subsequently demonstrated that administration of adenosine deaminase, which lowers the levels of endogenous adenosine, prevented the attenuation in coronary vasoconstrictor response to sympathetic nerve stimulation following ischaemia in dogs [10]. These findings indicate that exogenous adenosine reduces cardiac neurotransmission and that endogenous adenosine is involved as a mediator of neuronal stunning. The role of adenosine has been further clarified in the elegant study by Burgdorf et al. [11] in this issue of Cardiovascular Research. In the isolated perfused rat heart, the exocytotic release of noradrenaline induced by electrical field stimulation was progressively suppressed by increasing periods of ischaemia. In accordance with previous studies, both the degree and the duration of impaired noradrenaline release were dependent on the duration of ischaemia. A non-selective adenosine receptor antagonist prevented the suppression of noradrenaline release when the antagonist was given both during ischaemia and reperfusion but not when it was given during reperfusion only. This finding supports the concept that adenosine mediates the attenuation of noradrenaline release, and in addition demonstrates that this effect is mediated during the ischaemic period. Burgdorf and co-workers further show that the effect is mediated via activation of the adenosine A1 receptor subtype since the suppressed noradrenaline release was prevented by a selective adenosine A1 receptor antagonist but not by adenosine A2 or A3 receptor antagonists. The involvement of the adenosine A1 receptor is further supported by the observation that a selective adenosine A1 receptor agonist, but not adenosine A2 or A3 receptor agonists, suppressed noradrenaline release in
normoxic hearts. An important finding is that the suppression of noradrenaline release by the adenosine receptor agonist R-PIA persisted at least 5 min after removal of the agonist. This finding supports the notion of adenosine being the mediator of neuronal stunning which is characterized by a long duration. For comparison, the suppression of noradrenaline release evoked by pre-junctional α1-adrenoceptors did not persist following withdrawal of the α2-adrenoceptor agonist. Moreover, blockade of α2-adrenoceptors did not affect the post-ischaemic suppression of noradrenaline release, which indicates that noradrenaline acting on pre-junctional α2-adrenoceptors is unlikely to be a mediator of neuronal stunning. Taken together, this study clearly suggests that neuronal stunning is mediated by adenosine formed during the ischaemic period and that it acts by stimulating pre-junctional adenosine A1 receptors which results in prolonged reduction of exocytotic noradrenaline release.

A limitation of the study by Burgdorf et al. [11] is that the release of noradrenaline was not related to any functional responses. It is therefore not known how the suppressed release of noradrenaline affected nerve-mediated changes in myocardial contractility or coronary vascular resistance. In a previous study by Abe et al. [12], a non-specific adenosine antagonist, a specific adenosine A1 receptor antagonist as well as an adenosine A2 receptor antagonist prevented the post-ischaemic attenuation of sympathetic coronary vasoconstriction in dogs. Furthermore, the combined administration of an adenosine A1 and an adenosine A2 receptor agonist, but neither agonist alone, attenuated subsequent coronary constriction elicited by sympathetic nerve stimulation [12]. The conclusion from that study was that more than one adenosine receptor subtype may be involved in the development in neuronal stunning affecting the coronary vasoconstrictor response to sympathetic nerve stimulation. It is very likely that species differences exist which may explain the different results in the rat heart and in the dog. In addition, the release of noradrenaline was not determined in the study of Abe et al. [12] and it may be important to determine both transmitter release and the functional response evoked by the transmitter to fully clarify the situation.

The exact mechanism by which adenosine mediates neuronal stunning is not fully understood. The study by Burgdorf et al. [11] indicates that it is mediated via a presynaptic action of adenosine acting on adenosine A1 receptors. It has in addition been demonstrated that nerve growth factor (NGF) exerts a protective action against ischaemia-induced neuronal stunning [13]. NGF activates protein kinase N, a serine protein kinase which may be inhibited by adenosine. The neuronal protection induced by NGF may indirectly be mediated by the action of adenosine on serine protein kinase. Thus, the adenosine-induced neuronal stunning may involve NGF.

What are the potential clinical implications of neuronal stunning? Post-ischaemic neuronal stunning may be beneficial by reducing sympathetic coronary vasoconstriction and thereby reducing myocardial ischaemia. On the other hand, sympathetic activation may be protective during periods with restricted coronary flow by redistributing blood flow from the subepicardium to the subendocardium [14]. Neuronal stunning would thereby inhibit this favourable transmural distribution of blood flow. Furthermore, neuronal stunning affecting both sympathetic and vagal nerves may produce regional autonomic imbalance which could predispose to ventricular tachyarrhythmias. Finally, neuronal stunning of cardiac afferent nerves may reduce pain perception which will contribute to silent myocardial ischaemia. Neuronal stunning may thus be of importance for the functional consequences of reversible myocardial ischaemia. Studies like the one by Burgdorf et al. [11] which increase our understanding of the mechanism behind neuronal stunning are therefore important in order to evaluate the consequences of neuronal stunning and to develop tools to prevent its potential negative effects.

References