



Editorial

Adrenaline: More than a century after its discovery and still a mystery

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Adrenaline, also known as epinephrine, is traditionally involved in the “fight-or-flight response” [1]. Adrenaline was discovered at the end of the nineteenth century and isolated at the beginning of the twentieth century [2]. The catecholamines adrenaline and noradrenaline are the major effectors of the adrenergic nervous system [3]. They are synthesized by enzymatic conversion of dopamine to noradrenaline by the action of dopamine-hydroxylase. Noradrenaline is stored in vesicles for release into the synaptic cleft of neurons after stimulation by adrenergic nervous impulse [4]. Noradrenaline can be converted to adrenaline by phenylethanolamine-N-methyltransferase (Pnmt), a cytoplasmic enzyme [3]. Adrenaline is mainly synthesized in adrenal medulla and released to the bloodstream; other tissues, such as the heart and blood vessels also have Pnmt and can synthesize adrenaline [5–7]. Adrenaline and noradrenaline interact with α - and β -adrenergic receptors to mediate most cardiovascular effects of catecholamines [4].

Cardiac β -adrenergic receptors are mostly β_1 subtype, whose stimulation increases chronotropism and inotropism; most noncardiac receptors are β_2 [4]. The α -adrenergic receptors α_1 and α_2 are predominantly located in blood vessels. In peripheral and coronary arteries, the α_1 -adrenergic receptor mediates constriction, while the β_2 -adrenergic receptor mediates dilation. In β_1 receptors, adrenaline and noradrenaline have a similar potency; in β_2 receptors, adrenaline is more potent than noradrenaline [5]. The α_1 -agonist potency of noradrenaline is higher than that of adrenaline [4].

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Despite extensive studies on the role of catecholamines, the importance of adrenaline to the cardiovascular system at rest and during stress is still not completely understood. Previous studies have evaluated animals subjected to adrenal medullectomy, which can injury the adrenal cortex and jeopardize release of corticosteroids and other hormones. Furthermore, peripheral tissues might synthesize adrenaline to stimulate adrenergic receptors locally [5]. Other researchers have used Pnmt inhibitors, that besides blocking adrenaline synthesis can also inhibit other catecholamine processes and α_2 -receptors [7]. Only more recently, was an adrenaline-deficient mouse model generated by selectively knocking out the Pnmt gene (Pnmt-KO) [3]. This animal cannot produce adrenaline, but is able to synthesize and maintain normal plasma levels of noradrenaline [5,8]. Studies have shown that Pnmt-KO mice survive to adulthood and breed effectively [3]. Also, cardiac evaluation by echocardiogram did not reveal any abnormalities and the ability to run on a treadmill was preserved [5]. However, as adrenaline release from the adrenal medulla is one of the first responses to stressors, including physical exercise, it was suggested that Pnmt-KO mice would have an abnormal cardiovascular response to chronic exercise [5].

In this issue of the *International Journal of Cardiology*, Mendes and colleagues provide us with an extensive cardiac evaluation of sedentary and exercised Pnmt-KO mice. In an approach combining echocardiographic evaluation and *in vivo* hemodynamic analysis, the authors show that sedentary Pnmt-KO mice present slightly increased arterial blood pressure and systemic vascular resistance with concentric left ventricular (LV) remodeling, and decreased LV compliance and cardiac output. Despite preserved LV functional indexes, *in vivo* cardiac response to β_1 -adrenergic agonist dobutamine was blunted.

Exercised mice were trained on a treadmill 5 days/week for 6 weeks at a final speed of 20 m/min for 55 min. After chronic adaptation to exercise, Pnmt-KO mice maintained slightly increased arterial blood pressure, but presented a robust concentric LV hypertrophy. LV compliance was increased by exercise. LV functional parameters including load-independent indexes of cardiac performance were unchanged; *in vivo* cardiac response to dobutamine remained blunted. To better characterize LV hypertrophy, the authors evaluated myocardial gene expression of insulin-like growth factor (IGF)-1 and atrial natriuretic peptide (ANP), which were increased in exercised Pnmt-KO mice compared to both sedentary Pnmt-KO and exercised wild type (WT) groups.

The marked LV hypertrophy, increased ANP gene expression, and impaired response to dobutamine suggest for the first time that the lack of adrenaline is responsible for the development of pathological hypertrophy under chronic physical exercise.

The mechanisms involved in the blunted cardiac response to dobutamine in Pnmt-KO mice are not clear. It might be related to an impaired dobutamine-induced vasodilation through β_2 -adrenergic receptors. This hypothesis is supported by Moreira-Rodrigues et al., who observed that Pnmt-KO mice present a lower β_2 -adrenoceptor protein density in aorta cell membranes than their WT counterparts [8]. Another possibility for the blunted response to dobutamine is a decrease in myocardial contractile reserve. As previously reported, most cardiac β -adrenergic receptors are the β_1 subtype. However, about 20% of the total receptor population in the heart is the β_2 subtype, which is more responsive to adrenaline than noradrenaline [4]. Therefore, it is possible that a chronic lack of adrenaline stimulation could change myocardial β -adrenergic receptors and reduce myocardial contractile reserve.

The reason for the robust LV hypertrophy after chronic exercise is also unknown. Chronic running induces LV hypertrophy [9,10]. However, exercised Pnmt-KO mice had substantially more hypertrophy than WT mice (increase in LV mass index of 52% in WT vs 170% in Pnmt-KO mice). The pathological nature of the exacerbated LV hypertrophy in Pnmt-KO mice was reinforced by the increased ANP gene expression in myocardium. As pointed out by the authors, an increase in afterload may be involved in the marked hypertrophy. Since adrenaline stimulation of β_2 -adrenoceptors is more potent than that induced by noradrenaline, and Pnmt-KO mice present lower vasodilator β_2 -adrenoceptor density [8], Pnmt-KO mice may have been subjected to higher blood pressure during chronic exercise. In fact, it has previously been shown that Pnmt-KO mice develop higher blood pressure during acute exercise than WT mice [5]. However, a component of independent afterload LV hypertrophy cannot be discarded in this study.

This study adds important information on the role of the adrenergic nervous system during physiologic conditions at rest and after chronic exercise. The authors emphasize that conversion of noradrenaline into adrenaline appears to be necessary for preventing pathological cardiac hypertrophy in chronic exercise. Additional studies are needed to better characterize pathological LV hypertrophy in exercised Pnmt-KO mice and to establish the role of adrenaline under pathological cardiac remodeling such as after myocardial infarction and chronic arterial hypertension.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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