DHEA treatment of pulmonary hypertension: New insights into a complex mechanism

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Pulmonary arterial hypertension (PAHT) is an implacable killer. Patients developing PAHT present a survival rate of 40% after 36 months [1]. This deadly pathology remains actually an orphan in terms of long-term treatment and affects more than 100,000 patients in the United States and Europe, with an annual incidence estimated at 2 new cases for primary PAHT and 8 new cases for secondary PAHT per million individuals per year.

Pulmonary hypertension is classified into two main categories. The causes of primary PAHT remain largely unknown, but new studies have identified a gene located on chromosome 2 coding for bone morphogenetic protein receptor I (BMPR2), which belongs to the transforming growth factor β type-II receptor family, and inhibits cell growth. A mutation responsible for 6% of primary PAHT induces an abnormal response of the vascular endothelium to injury, leading to cancerous-like proliferation of endothelial cells [2].

Secondary PAHT has many causes that may vary from a prophylaxis reaction [3] to potassium current alterations like the decrease of Kv1.5 subunit expression in smooth muscle cells (SMC) induced by consumption of anorectic agents. Nevertheless, the most common source of secondary PAHT remains chronic obstructive pulmonary disease (COPD), which is expected to become the fifth greatest cause of mortality by 2020 with a 10-year survival rate of 50% after diagnosis. An estimate in the 1990s indicates 16 million cases in the United States, and 1.2 million hospitalisations for COPD in the UK [4]. These numbers clearly demonstrate the importance of studies like those of Oka et al. [5] presented in this issue and the necessity of developing new treatments.

Dehydroepiandrosterone (DHEA) was isolated for the first time in 1934 by Butenandt and Dannenbaum and extracted from human plasma later in 1944 by Migeon and Plager [14]. DHEA is a 3b-hydroxysteroid metabolised from pregnenolone [15] and its secretion from the adrenal gland decreases with ageing for humans and primates [16]. There is actually a controversy about the plasma levels of DHEA and DHEA-sulphate in cases of coronary atherosclerosis; some studies find it increased but others show a decrease [17,18]. Nevertheless, DHEA has many interesting properties: it has been shown to dilate arteries, to block hypoxia-induced vasoconstriction by activating potassium channels via soluble guanylate cyclase (sGC) activation [19], and to enhance.
endothelial function in particular through increased nitric oxide synthesis [20]. To date, the physiological role of DHEA remains largely unknown, but it is seen by many as a potential “fountain of youth” and is freely available online as a nutritional supplement. New studies are thus overdue for the understanding of DHEA’s endogenous regulatory role in the circulation and its potential use for PAHT therapy, as well as for discerning more of the physiological effects observed for a wider range of concentrations of DHEA intake [5].

In this issue of the Journal, Oka et al. [5] have investigated the many aspects DHEA treatment has on hypoxia-induced pulmonary hypertension, and the results are promising in terms of providing leads to developing new therapies. Chronic treatment of pulmonary hypertensive rats with DHEA induces an increase of testosterone plasma levels. In return, testosterone is known to increase the carotid body sensitivity to hypoxia and to stimulate the ventilatory response to hypoxia and hypercapnia [21]. One point to consider is the effects on cardiac output observed with increasing concentrations of DHEA, especially the fact that the systolic index, which is not much different between pulmonary hypertensive rats treated or not with 1% DHEA, shows a tendency to increase back to a normal value for a treatment with 0.3% DHEA, which in contrast is less efficient against PAHT. This suggests a possible dual cardiovascular regulatory potential of DHEA with an effect on heart functionality itself, which needs further investigation especially considering the lack of regulation in the DHEA market.

Some very interesting findings were made by using DHEA not only to inhibit the development of PAHT, but to treat established PAHT [5]. Indeed, this team succeeded in recording an inhibition of PAHT, and more importantly a remission of well-established PAHT correlated with a decrease of physiological consequences on heart function and pulmonary artery remodelling. This effect seems to be due to an increased expression and activity of sGC, which increases the arterial wall response to nitric oxide, thus compensating the endothelial dysfunction induced by PAHT.

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References


