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COMMENTARY

Hormesis, mithridatism and Paracelsus: A little oxidative stress goes a long way

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Paracelsus is quoted as saying 'All things are poison and nothing is without poison; only the dose makes a thing not a poison'.

This concept seems to be germane to the review article by Dekleva *et al.*,[1] in this issue of *Hypertension Research*. Specifically if a poison in humans is defined as toxic at >50 mg kg or as little as 3.5 g in a 70 kg adult,[2] oxygen radicals may be one of the most potent poisons on Earth as even an entire liter of oxygen only weighs 1.34 g, and oxygen radicals make up only a very small fraction of the total molecules. Oxygen flow through the tissues (muscle, blood vessels, heart, cerebral circulation and so on) creates reactive oxygen species (ROS), and these can be very toxic to proteins, lipids, transport molecules, cell membranes, and, of course, nuclear and mitochondrial DNA. Aging, cell death, apoptosis and degradation of tissues from within may all be related to ROS, so controlling the amount and location of these 'bad actors' is clearly important. If Mithrades is to be believed, he took small doses of poison so that he would be immune to large-dose poisoning by his courtiers (the notion of hormesis). The story of ROS may be a similar situation. Small doses are not only not harmful to the overall organism, but indeed may be required to continue to stimulate the balance between oxidants (superoxides, hydroxyls and hydrogen peroxide generated from xanthine oxidases, NADPH oxidases and cytochrome P450) and antioxidant subsystems, such as superoxide dismutase, catalase and glutathione reductase.

Dekleva *et al.*[1] explored the notion of hormesis in hypertension in relation to the interaction between acute exercise (stimulating ROS production and oxidative stress) and its ensuing chronic adaptive response (to increase antioxidant scavengers and better defend against future insults). Indeed, there is a long-established link between high aerobic capacity (VO_2 peak) and survival, both in normals and in patients with a wide range of chronic disease.[3–7] Thus, to assign ROS as 'bad actors' caused by excessive oxygen flux resulting in detrimental oxidative damage, would be to malign the vital role of redox signaling adaptive benefit. ROS are cellular redox signals to a variety of tissues that at once mitigate oxidant production and promote antioxidant expression and mitochondrial biogenesis that is beneficial to the organism.

Oxidative stress 'defined as a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses',[8,9] may be the result of inadequate quenching of ROS generated from energy production. In fact, hypertension (HTN) may also be driven by ROS, to the extent that ROS are released into the vascular wall and peripheral/central nervous system (neuronal signaling). Also, ROS may directly bind nitric oxide and prevent it from relaxing the vascular bed when cardiac output (and thus shear stress) is increased. The problem in humans is that ROS are devilishly difficult to detect while the organism is living, and is best detected in animal models where deep tissue can be more easily sampled in a timely manner. It has long been suspected that ROS in the heart may be responsible for fibrosis, ROS in the vascular system may promote coronary artery disease (CAD) and peripheral arterial disease (PAD), and ROS in the vascular system and heart may be responsible for both HTN and heart failure.[10]

Dekleva *et al.*[1] in this article reviews the research evidence (animal and human) regarding the link between oxidative stress and the development/progression of hypertension. She describes several experimental models of spontaneous hypertension (spontaneously hypertensive rats) and mitigation of ROS generation and blood pressure (reduction on the order of 3-5 mm Hg) with chronic exercise therapy. She specifically focuses on the role of exercise-induced oxidative stress, both single bout and chronic low-to-moderate exercise training. With regards to both animal and human data, she finds the evidence convincing that chronic exercise improves the mechanisms that support oxidative defense. Finally, she explores the available data on chronic intensive interval training modifications to the redox state in hypertensive patients.

Sustained aerobic exercise seems to reduce ROS effects and promote a reduction in blood pressure (although the opposite occur with acute exercise without exercise training). As such, it appears that chronic aerobic exercise (3× per week and 50–70% VO_2 peak) shows a reduction in mean arterial pressure, an improvement in aerobic capacity and beneficial changes in redox state. The mechanism for this is of course not clear, but if ROS are cellular signals they may be a potential mechanism to activate these effects in widely separated tissues and organ systems. Indeed exercise training decreases oxidized lipids, stimulates protein anabolism, reduces blood pressure and promotes health in a variety of ways.[11]

One of the more surprising findings in this review paper is that high-intensity interval training (HIIT) and endurance training have opposing effects on markers of heart failure

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and cardiac remodeling in hypertensive rats, even though HIIT clearly excels at inducing a potent training effect, increasing the lactic acidosis threshold and aerobic capacity in normal and in many chronic diseases. How can this paradox be reconciled? This would appear to be an excellent topic for future research, as the explanation does not seem to be immediately apparent from current evidence. Like all good research, the quest for knowledge is not a destination, it is a never-ending journey.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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