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EDITORIAL

Is your autonomic function good enough to be an Olympian? And other updates on recent autonomic research

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Is your autonomic function good enough to be an olympian?

> "There was no logic in my mind that if you can run a mile in 4 min, 1 and 2/5ths, you can not run it in 3:59. I knew enough medicine and physiology to know it wasn't a physical barrier, but I think it had become a psychological barrier."
> -Sir Roger Bannister (1929–2018)

As autonomic physicians we are accustomed to interpreting abnormal autonomic function, however, it can be equally instructive to understand the autonomic function in healthy individuals. In this regard, professional athletes are ideal subjects to study. Becoming a professional athlete requires not only dedication and countless years of training, but also underlying favorable genetic factors that influence overall achievement. Among the many factors that lead to superior athletic performance, near perfect autonomic regulation is essential. It is therefore reasonable to assume that professional athletes, with their finely tuned reflexes and physical abilities, might have superior autonomic regulation when compared to otherwise healthy individuals. To understand the differences in autonomic regulation between excellent athletes and those skilled enough to qualify for the Olympics, the *European Journal of Applied Physiology* published an interesting and topical work on autonomic regulation in these two athletic groups [1].

To test the hypothesis that athletes who qualify for Olympic events have superior autonomic and somatic stress measures, the authors performed a retrospective analysis of various clinical, autonomic and cardiovascular measures collected from Italian athletes leading up to the 2016 summer Olympic Games. They used the previously defined unitary multivariate percent ranked Autonomic Nervous System Index (ANSI). ANSI is derived from three different measures including the R–R interval, RR variance and rest to stand differences in the low-frequency component of RR variability in normalized units. They retrospectively reviewed data from 778 athletes (mean age 24.4 years). As a part of pre-participation screening, all athletes underwent a complete history and clinical evaluation, including heart rate variability at rest and with standing, bicycle ECG stress testing and a subjective stress symptom profile questionnaire.

Athletes were divided into those who qualified for the 2016 summer Olympics in Rio de Janeiro (Rio+, $N=238$) and those who did not (Rio-, $N=540$). Rio+ athletes were older (26.48 vs 23.49 yrs) and had a slightly lower resting HR (57 vs 60 bpm). There was no difference in BP or other anthropometric data. Rio+ athletes also had a higher mean RR and higher indices of RR recovery after exercise. ANSI was significantly higher in Rio+ athletes compared to the Rio- group, and more so in the group of athletes who participated in high intensity training. Overall somatic stress symptoms were low in all athletes and lower in the Rio+ group.

Overall, this retrospective analysis emphasizes the important role that cardiac autonomic regulation plays in athletic performance, and the potential use of a unifying autonomic index to measure cardiac autonomic regulation. It is important to note that this study was not designed to validate a single autonomic index as a screening tool to differentiate those destined to become Olympians from other athletes. A long-term, prospective evaluation of ANSI in athletes as they train over many years to become Olympic athletes would be better suited to answer this question. This type of study would allow us to understand if this index, or ones

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like it, can be improved by training, and, if so, what type of training could lead to improved performance. Very soon there might be even be a smartphone app that mere mortals like us can use to compare our autonomic regulation with these superhuman athletes.

Not all alpha-synuclein is created equal

It is now well established that the pathology of Parkinson disease (PD) results from the deposition of α-synuclein in the form of Lewy bodies (LB) and Lewy neurites in the central nervous system (CNS) and the peripheral nervous system (PNS), including the peripheral autonomic nerves. What is less clear is why α-synuclein favors certain neuroanatomical areas in the CNS and PNS, in what sequence it is deposited as the disease progresses, and to what extent the autonomic nerves are involved. One theory involves a peripheral to central mechanism, whereby α-synuclein is first deposited in the peripheral somatic and autonomic nerves and progressively spreads to the CNS through synaptically-connected networks in a prion-like fashion, inducing neuronal cell death in the process [2].

Supporting this hypothesis, research has demonstrated that purified LB containing α-synuclein from the substantia nigra pars compacta (SNpc) of mice with PD is able to induce pathological α-synuclein pathology and neurodegeneration when injected into the brains of healthy wild-type mice. The role of peripheral α-synuclein spread, however, is less well understood. In a recent study published in *Acta Neuropathologica Communications*, [3] researchers evaluated the pathogenic potential of peripheral α-synuclein aggregates by injecting LB extracts of human PD patients into the SNpc of wild-type mice. The unique aspect of this study was the fact that the researchers used LB obtained from the stellate ganglia, a peripheral paravertebral sympathetic ganglion that consistently exhibits LB pathology in patients with PD. Human postmortem samples from the stellate ganglia of three patients with sporadic PD and two age-matched non-PD control subjects were obtained from a neurological tissue bank. No α-synuclein pathology was observed in the stellate ganglia of the control subjects. Six months after inoculation, all animals were subjected to behavioral and histological analyses.

Motor testing was performed using a cylinder test, and no motor abnormalities were observed in the injected mice. The researchers then assessed the integrity of the dopaminergic nigrostriatal system in these animals by various immunohistochemical techniques and found no nigrostriatal degeneration in the brains of the injected animals. In addition, there was no evidence of inflammatory changes, as evidenced by lack of microglial and astrocytic reactions. The researchers did confirm that the LB extracts were internalized by the SNpc neurons in the wild-type mice, but not in the control-injected animals. They also found that the α-synuclein was susceptible to proteinase K digestion, indicating that it had not assumed a pathological insoluble beta-sheet conformation, as LB in the CNS typically do. In addition, no changes in hyper-phosphorylated pathological forms of α-synuclein were found between LB injected mice and control-injected mice at 6 months.

There are some limitations to this study. It is possible that other tissues containing LB may behave differently than the stellate ganglion tissue, and other sites were not sampled. The sample size of patients ($n = 3$) was quite small, and there is a large degree of clinical heterogeneity in PD. The LB homogenates obtained were from patients with end-stage disease, and patients with more active earlier disease may have LB that behaves differently. Nonetheless, this is a very interesting study that raises the possibility that not all α-synuclein is equal in its potential for pathogenesis, at least when it comes to cell-to-cell transmission of α-synuclein from the periphery to the CNS.

Do adrenergic receptors drive α-synuclein pathology?

The β2-Adrenoreceptor (β2AR) is best known for its role in sympathetic transmission; however, it has also been identified as a regulator of the α-synuclein gene (SNCA), an important gene involved in the development of Parkinson's disease (PD). Mutations of SNCA have been associated with an increase in the transcription of α-synuclein by 50-100%, which is then deposited in the form of Lewy bodies (LB) in familial PD [4]. As in Alzheimer's disease and other proteinopathies, many pharmaceutical companies have focused their drug development on compounds that might clear abnormal accumulations of these proteins, rather than prevent their production. In their paper entitled "β2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease," published in the September 1, 2017 edition of *Science*," Mittal and colleagues explore this theory [5].

In prior studies, the authors found that β2AR activation in mice induced parkinsonism. In the current study, they explore a potential mechanism. They developed a high-throughput gene expression assay for endogenous human SNCA expression in neuronal cells (human SK-N-MC neuroblastoma cells), with which they tested various β-agonists and measured SNCA mRNA levels. They found several medications that decreased SCNA expression (metaproterenol, clenbuterol, salbutamol, riluzole). They then tested antibodies against α-synuclein to determine whether the modulation of SNCA mRNA expression by β2AR translated to changes in α-synuclein protein levels. They found that

β2AR agonists lowered SCNA expression and α-synuclein protein in a dose- and time-dependent manner.

The authors therefore propose a model whereby β2AR antagonists increase SNCA expression through acetylation, which results in the accumulation of α-synuclein and cell damage. By this theory, β2AR agonists should reduce SNCA expression through deacetylation, and help protect against cell damage. There are some data supporting this theory; for example the β2AR agonist salbutamol has been associated with a reduced risk of PD, whereas the β2AR antagonist propranolol has been associated with increased risk. This theory deserves further study, as strong evidence would be necessary to change prescriber practices. Many β-blockers are prescribed for cardioprotective effect, which many elderly patients in PD require; conversely, β-agonists could potentially exacerbate cardiovascular risk. This should not prevent exploration of this mechanism. In light of certain drug companies' recent decision to halt all development of PD and Alzheimer's research due to lack of positive data, the drug development pipeline needs more mechanisms to explore. This is one such mechanism that holds this potential.

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Compliance with ethical standards

Conflict of interests None.

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