

## **Sarin produces delayed cardiac and central autonomic changes.**

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Department of Pharmacology and Toxicology, Boonshoft School of Medicine, Wright State University, 3640 Colonel Glenn Highway, Dayton, OH 45435, USA. The aim was to evaluate the acute and delayed effects of low dose sarin exposure on cardiac autonomic and brainstem catecholaminergic function in mice. The rationale was to expand our knowledge of the cardiovascular effects of this neurotoxic, acetylcholinesterase (AChE) inhibitor. C57BL/6 male mice with telemetric arterial catheters were injected with saline or sarin (8 µg/kg, 0.05x LD<sub>50</sub>; sc, two injections) with blood pressure (BP) measurements made at 1 and 10 weeks after sarin exposure. BP and pulse interval variability (PI) and low and high frequency spectral oscillations were measured using autoregressive spectral analysis. In situ hybridization (ISH) was used to quantify tyrosine hydroxylase (TH) mRNA expression in brainstem cardiovascular centers. Sarin had no effect on blood AChE activity, heart rate (HR) or BP. There was a biphasic response in PI variance, an early increase (+140%) and a delayed decrease (-62%) at more than 2 months after sarin exposure. There were no changes in BP variance. Assuming that increased PI variance is a positive outcome, the short-term response to sarin should be protective. This is opposite for the delayed decrease in PI variance which is associated with adverse cardiovascular effects. There was an increase in TH mRNA in both locus coeruleus (0.18±0.05 vs. 1.4±0.2 µCi/g; control vs. sarin) and dorsal vagal complex (0.09±0.06 vs. 1.17±0.03 µCi/g; control vs.

sarin). Results show that a dose of sarin which had no peripheral cholinergic effects caused changes in autonomic modulation, a short-term enhancement followed by a delayed impairment in heart rate variability. Sarin-induced cardiac effects suggest a controversial aspect to the use of pharmacological agents which target AChE for management of cardiovascular risk.

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