

## Nerve gas antidotes

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Organophosphorus nerve gases such as sarin, soman and VX act mainly by inhibiting cholinesterase at cholinergic synapses. The consequent accumulation of acetylcholine results in muscle twitching, glandular hypersecretion and cognitive and mood effects. High doses cause seizures and death from respiratory failure. Nerve agents affect both main types of cholinergic receptor—muscarinic and nicotinic.<sup>1</sup>

Treatment of nerve agent poisoning at present relies on two approaches. In the first, an oxime is given to detach the agent from cholinesterase, thus reactivating the enzyme.<sup>2</sup> This mitigates both nicotinic and muscarinic effects, for those nerve agents against which oximes are effective (which do not include soman). In the second, the muscarinic antagonist atropine is used to quell the effects of excessive acetylcholine action. Atropine is of special value when the nerve agent is oxime-resistant or when symptoms are already severe. However, atropine targets only excessive muscarinic activity. What about the nicotinic effects? These too are surely important yet seem to be neglected in the published work. We found no mention in conventional sources, in numerous declassified US Department of Defense documents or in about fifty UK Ministry of Defence documents declassified expressly to allow work issues related to nerve agent protection. Nicotine is a convulsant poison,<sup>3,4</sup> and nerve agents enhance nicotinic depolarizations<sup>5</sup> and modulate nicotinic receptor ion channels directly by an allosteric effect<sup>6,7</sup>—as does pyridostigmine,<sup>8</sup> which is used as a protective measure against nerve gases. Khan *et al.*<sup>9</sup> injected rats intramuscularly with sarin and examined the brains at intervals afterwards (up to 20 h). They noted a biphasic effect on ligand binding (reduced at 1–3 h and increased at 6–12 h) which was much stronger at nicotinic receptors than at muscarinic receptors.

More importantly, published evidence suggests that organophosphate exposure causes persistent changes in both

muscarinic and nicotinic function. With repeated low-level exposure chronic changes have been reported in muscarinic (M1 and M3) receptors.<sup>10</sup> But, in addition, persistent downregulation of nicotinic receptor expression has been demonstrated in rats exposed to a cholinesterase inhibitor.<sup>11</sup> These changes were associated, in the animals, with impaired function on cognitive tests, and the nicotinic character of the impairments was confirmed by reversal with nicotine.

Thus it would seem appropriate to examine nicotinic antagonists as well as muscarinic ones, as possible therapeutic agents for anticholinesterase nerve gas toxicity.

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