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Neuropathic Aspect of Organophosphate Toxicity: A Review

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Abstract: Organophosphates (OPs) are known to produce a delayed neuropathy in man and domestic animals. Other than acute cholinergic toxicity of OPs, they have been known to cause a delayed neuropathy called Organophosphorus Induced Delayed Neuropathy (OPIDN). Clinical manifestation of OPIDN is characterized by a delay period which is observed between 8 to 14 days after dosing. Toxic signs induce flaccid paralysis of lower and upper limbs and changes in neurons defined as a central-peripheral distal sensory-motor axonopathy. Although the mechanism is not clearly understood, OPs toxicity is attributed to inhibition of NTE. The initiation of OPIDN requires inhibition of NTE. Methods to elucidate mechanism of the toxicity may include use of other chemicals which can potentiate or prevent toxicity. Phenylmethylsulfonyl Fluoride (PMSF) is one such agent which has been widely utilized in mechanistic studies of OPIDN. Phenylmethylsulfonyl fluoride is a serine protease inhibitor which has been used to elucidate the mechanism of OP induced delayed neuropathy. Phenylmethylsulfonyl fluoride prevents OPIDN when given prior to an OP compound, but if PMSF is administered after an OP compound it potentiates the neurotoxicity.

Key words: Organophosphates, delayed neuropathy, neuropathy target enzyme, PMSF

INTRODUCTION

Many Organophosphorus (OP) toxicants irreversibly inhibit the enzyme acetylcholinesterase. Acetylcholinesterase normally degrades acetylcholine into choline and acetic acid at cholinergic synapses. Organophosphate poisoning thus causes the accumulation of acetylcholine, allowing it to react with nicotinic and muscarinic receptors on the postsynaptic cells. The resultant effect is manifested by excess stimulation of cholinergic nerves with related symptoms such as excessive secretions and convulsions. The cholinergic effect of OP is a well known aspect of OP poisoning. However, neuropathy is another possible consequence of OP exposure. A single dose of some OPs is enough to cause irreversible neuropathy 2-3 weeks after exposure[1]. This effect of OP poisoning is referred to Organophosphate Induced Delayed Neuropathy (OPIDN). Earlier in the elucidation of mechanism of the OPIDN, it was thought that brain acetylcholinesterase and butyrylcholinesterases might be involved in the mechanism of OPIDN. Later it was found that organophosphate induced delayed neuropathy has no relation to the inhibition of acetylcholinesterase[2]. The neurotoxic effect was then found to be associated with phosphorylation of a brain protein called neuropathy target esterase (NTE) by certain OPs[3,4]. Interestingly, while some OPs are able to inhibit NTE and cause OPIDN, some OPs, carbamates and phenylmethylsulfonyl fluoride have the ability to inhibit the enzyme, but they are unable to produce OPIDN[5]. Furthermore, studies showed that the neurotoxic effect of neuropathic OPs can be prevented or potentiated with the administration of these non-neuropathic NTE inhibitors in a sequence dependent manner[6,7].

Chemistry of organophosphorus compounds: Although organophosphorus compounds show great diversity in details of their chemical structure, they have common backbone. Organophosphorus are aliphatic carbon, cylic, or heterocylic phosphodiesters[8].

Pentavalent phosphorus posses double bond with either a sulfur or an oxygen (S=O is capable of inhibiting esterases). Side groups can vary and bind to the phosphorus either directly (phosphinates), via an oxygen (phosphates) or via nitrogen (phosphoroamidates)[9].

Interactions of organophosphorus compounds with target esterases: Esterases can be divided into two groups which are A esterases and B esterases. A esterases detoxify Ops while B esterases are inhibited by OPs and the latter comprises target esterases (e.g. Acetylcholinesterase) in the body. The active site of the esterase, serine hydroxyl group, is phosphorylated and the active site is then slowly reactivated by hydrolysis. A subsequent reaction might take place after phosphorylation called aging, however which leaves a negatively charged phosphoryl residue leading to irreversible inhibition of the enzyme[9].

Role of neuropathy target esterase enzyme (Nte) in organophosphorus induced delayed neuropathy: After the discovery of NTE, extensive research has focused on the role of NTE in the initiation of OPIDN. Involvement of NTE in OPIDN was first discovered with the use of non-neuropathic NTE inhibitors. Some chemicals such as PMSF (serine protease inhibitor) and carbamates showed strong inhibitory effect on NTE *in vivo*, but without producing neuropathy. However, when animals were co-exposed to these chemicals were applied with neuropathic OPs, it was noted that neuropathy induced by OPs can be either protected or potentiated depending on the sequence of application[10]. Johnson[11] proposed that certain non-neuropathic NTE inhibitors (PMSF) given prior to neuropathic OPs have protective effect from OPIDN in spite of its extensive inhibitory effect on NTE. Interestingly, given after a neuropathic OP, PMSF promotes the neuropath[6]. It was postulated that initiation occurs by a two step process. The first step includes phosphorylation of active site of NTE and the second step includes "aging" leading to alteration in membrane micro environment and disturbance of homeostasis causing degeneration of long axons. In the protection it was postulated that the second step does not occur because PMSF and carbamates are not capable of aging. Secondly, as a result of occupation of NTE's active site by these compounds the enzyme is protected from neuropathic agent[4,10]. Young chickens are resistant to OPIDN[5], but PMSF can increase sensitivity to OPIDN[3,6,10]. It was postulated that NTE may not be involved in promotion of OPIDN. Higher doses of neurotoxic OPs show no effect in young chickens despite the inhibition of NTE which is enough to induce OPIDN in adult chickens. However, young chicks become sensitive with PMSF following the neuropathic agent. These studies suggested that NTE may not be the target for promotion[12,13].

Neuropathy target esterase: Neuropathy target esterase is a protein which is found in many tissues. The highest concentration of the enzyme was reported to be in the brain, whereas most of the esterase activity is membrane bound mainly in the endoplasmic reticulum and plasma membrane. Neuropathy target esterase can also be found in different tissues other than nerve tissues. For example, NTE was found in spleen and lymphocytes in higher concentrations[2]. Despite extensive study, little is known about the physiological role of NTE. Even with long term inhibition by phosphinates and sulfonyl halides (PMSF) NTE inhibition did not cause OPIDN. Therefore, no correlation has been found between the NTE inhibition and well-being of a neuron[14]. Primary sequence of human NTE and mouse NTE has high similarity to swiss cheese protein (SWS) in nerves of Drosophila melonagaster. Flies without this protein are affected by glial hyperwrapping and neurodegeneration. A recent article showed for the first time NTE is essential for embryonic development in mice. Genetic ablation of NTE in mice resulted in hyperactivity and it was suggested that NTE may play a role in motor activity in mammals[15].

Clinical and histopathological presentation of OPIDN: Clinical manifestation of OPIDN is characterized by a delay period which is seen between 8 to 14 days after dosing. The hen has been the animal model in studies of OPIDN to characterize the clinical expression of OPIDN in animal species. Hens given a single dose of 1 mg kg^{-1} diisopropyl flurophosphate start to show first sign of ataxia after 8 days following dosing with slight incoordination and leg weakness. Then ataxia progresses with time and complete ataxia and marked paralysis of the legs develop by day 13[16]. The delayed neurotoxic effect of some OP compounds can be altered by the time dependent administration of PMSF. It has been shown that PMSF intensifies the ataxia when given following a neuropathic OP dosing. In addition, age is another factor in the clinical expression of OPIDN in response to OP treatment. Young chicks are known to be resistant to OPIDN. For instance, while 5 week-old chicks appeared normal in response to OP treatment, chickens receiving same treatment and dose of OP at 8 weeks age developed ataxia. Interestingly, young chicks (e.g. at 5 weeks of age) become sensitive to the same OP treatment with PMSF post treatment[12,13].

Lesions in affected animals are distributed in central and peripheral nerves. Within the CNS, the spinal cord is mainly affected with axonal degeneration. Axons appear fragmented and swollen and myelin around the axon is lost. In peripheral nerves, large and long axons are more susceptible to the damage induced by OPIDN. Changes in peripheral nerves include focal nerve fiber varicosities and paranodal demyelination in the distal part of the nerves. The changes in central and peripheral nerves are defined as a central-peripheral distal sensory-motor axonopathy since distal parts of long axons are mainly affected[9,17].

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