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Review

Central respiratory failure during acute organophosphate poisoning☆

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ABSTRACT

Organophosphate (OP) pesticide poisoning is a global health problem with over 250,000 deaths per year. OPs affect neuronal signaling through acetylcholine (Ach) neurotransmission via inhibition of acetylcholinesterase (AChE), leading to accumulation of Ach at the synaptic cleft and excessive stimulation at post-synaptic receptors. Mortality due to OP agents is attributed to respiratory dysfunction, including central apnea. Cholinergic circuits are integral to many aspects of the central control of respiration, however it is unclear which mechanisms predominate during acute OP intoxication. A more complete understanding of the cholinergic aspects of both respiratory control as well as neural modification of pulmonary function is needed to better understand OP-induced respiratory dysfunction. In this article, we review the physiologic mechanisms of acute OP exposure in the context of the known cholinergic contributions to the central control of respiration. We also discuss the potential central cholinergic contributions to the known peripheral physiologic effects of OP intoxication.

1. Background significance

Organophosphates (OP) poisonings are a major worldwide health problem. It is estimated that there are more than three million cases of OP pesticide poisonings and over 250,000 deaths annually from intentional self-poisonings, representing 30% of suicides globally. OPs are used for pesticide control in developing countries, and a majority of these exposures occur in agrarian societies where they are readily available (Eddleston et al., 2008; Gunnell et al., 2007). Exposure to OPs may also come in the form of terrorist attacks with "nerve agents." A deadly assault by release of sarin gas was carried out in the Tokyo subway system in 1995, killing eleven people and harming hundreds (Okumura et al., 1996).

OPs act by inhibiting acetylcholinesterase (AchE) and exposure leads to accumulation of acetylcholine (Ach) within synaptic clefts. This results in overstimulation throughout the central and peripheral nervous system. In lethal exposures to OP agents, mortality is attributed to respiratory failure and pulmonary dysfunction (Tafuri and Roberts, 1987). Respiratory failure following acute OP poisoning is a multi-factorial process; it includes a direct depressant effect on the respiratory center in the brainstem, constriction of and increased secretion within the airways, and paralysis of the respiratory musculature (Bartholomew et al., 1985; Rickett et al., 1986).

Mortality following OP poisoning is as high as 40% even in the setting of highly sophisticated intensive care (Eyer et al., 2003). The standard therapeutic strategy includes decontamination, atropine, oximes, benzodiazepines and supportive care. Atropine and oximes are used to counteract the cholinergic symptoms but benzodiazepines are used to prevent seizure activities. However, despite widespread use of OP for the last 60 years and the health problems they generate worldwide, the therapy for acute OP exposure has not changed significantly for the last 50 years (Eddleston et al., 2008). In this article we focus on a review of the known physiologic mechanisms of acute OP exposure in the context of the known cholinergic contributions to the central control of respiration.

2. Organophosphate compounds

OPs are esters of phosphoric acid and are used as herbicides, insecticides, and nerve agents. Toxic exposure may occur through inhalation, transdermal absorption, or ingestion. The toxic effects of OPs are mediated through inhibition of the enzyme AchE, a serine protease that hydrolyzes the neurotransmitter Ach located in the neuromuscular junction and cholinergic brain synapses. Ach receptors are involved in transmission within the central, sympathetic, parasympathetic nervous systems and neuromuscular junctions and exert their actions via nicotinic or muscarinic

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Table 1
Respiratory data following dichlorvos poisoning in rat model.

Time	RR	MV	Vi
00:00	56 (12)	129.80 (45.6)	2.32 (0.64)
01:00	55.89 (12.9)	132.30 (45.4)	2.37 (0.59)
02:00	46.79 (25.4)	103.23 (77.0)	2.21 (1.13)
03:00	40.57 (29.2)	73.76 (53.3)	1.82 (0.97)
04:00	19.37 (19.7)	46.27 (52.0)	2.39 (1.41)
05:00	19.95 (21.8)	51.96 (66.6)	2.60 (1.33)
06:00	12.39 (16.1)	24.75 (41.9)	2.00 (1.00)

RR, respiratory rate; MV, minute ventilation; Vi, volume of inspired gas.
Summary data from 10 rats exposed to sub-cutaneous Dichlorvos (3× LD50) at 0 min. Adapted from Gaspari and Paydarfar (2009). Time represent minutes post dichlorvos exposure. Data presented as mean (stdev).

cholinergic receptors. Within the central nervous system, cholinergic transmission is integral to many functions, including aspects of respiratory control. Exposure to OPs results in the phosphorylation of the serine hydroxyl residue on AchE, blocking activity and resulting in the accumulation of Ach (Bajgar, 2005). Acute OP exposure produces increased Ach levels at the post-junctional receptors resulting in a variety of central and peripheral symptoms, including centrally mediated respiratory dysfunction. The mechanisms of the peripheral effects of OPs include hypotension (via muscarinic (Kullmann et al., 1982) and non-muscarinic mechanisms (Kojima et al., 1992)), weakness and paralysis (via effects on the neuromuscular junction (Wadia et al., 1987)), and muscarinic effects of bradycardia, vomiting, diarrhea, salivation, mydriasis, urinary incontinence, bronchoconstriction, bronchorrea and muscle fasciculations. Central effects include delirium, seizures and central respiratory depression, but the mechanisms of these effects are incompletely understood (Namba et al., 1971). Central apnea following acute OP exposure is predominately described in the laboratory animal. Table 1 demonstrates the respiratory effects of dichlorvos in a rat model. Apnea following OP human exposure is rarely described clinically as this rapidly leads to death outside the hospital. Central apnea is not typically seen in patients who survive to the intensive care setting because mechanical ventilation is used to treat respiratory insufficiency. However, it is plausible that the mechanism(s) contributing to OOP-induced central apnea in laboratory animals is also present in humans.

The actual symptoms that are present following an acute OP exposure relate to the specific OP, dose and route of exposure and co-ingestants. For example, the most common symptom following the Tokyo city subway bombing involving a dilute muco-cutaneous exposure of sarin was miosis (Okumura et al., 1996), but in a case series of severe OP poisonings, the most common symptom following a mixture of OP agents was respiratory failure (Peter et al., 2010).

There is evidence that OPs may also produce delayed, or chronic syndromes but this is not the focus of this review. Briefly, it is believed that recovery from acute OP exposure induces an "intermediate syndrome" consisting of peripheral and respiratory muscle weakness (Senanayake and Karalliedde, 1987). Neurological and psychiatric symptoms have also been described following OP exposure (Jamal, 1997; Page, 2003) but the mechanism of these effects is poorly understood. "Gulf War Syndrome" refers to the neurobehavioral changes observed in Veteran's and has been linked to the use of pesticides (Binns et al., 2008) but this is extremely controversial as the evidence for this association is poor.

3. Acetylcholine and the anatomy and physiology of normal respiration

A better understanding of how acute OP intoxication effects respiration can be obtained through an exploration of some of the components of respiratory control. Central control of the respiratory system contains a respiratory oscillator with both feedback and feed-forward afferent pathways along with efferent pathways. Afferent signaling provides the environmental cues that allow accurate control of respiration in a changing internal and external environment. Ach plays an integral role in respiration; almost every aspect of respiratory control contains or is influenced in some way by cholinergic mechanisms. There are cholinergic contributions to chemosensitivity (Nattie et al., 1989), efferent signaling to airways (Kc and Martin, 2010) and respiratory sub-mucosal glands (Wine, 2007), and vagal afferent signaling (Balan et al., 2011; Kubin et al., 2006) to name a few. It is not yet clear which of these mechanisms predominate during acute OP intoxication. Current models of respiratory control involve cholinergic neurons in multiple aspects of rhythm generation, including rhythm generation, afferent input and efferent output. See Lindsey et al. (2012) for review.

There is evidence that OP-induced central apnea requires a direct exposure to the brain, and that these effects are mitigated through muscarinic receptors. Rats exposed to paraoxon (an OP agent) were treated with atropine (an Ach competitive antagonist at muscarinic receptors and tertiary amine able to cross the blood brain barrier) or methylatropine (a similarly structured quaternary ammonium unable to cross the blood brain barrier)(Houze et al., 2008). In this model, atropine completely reversed the OP induced ventilatory effects whereas methylatropine did not, supporting a muscarinic role for central respiratory control. This study does not eliminate the possibility that peripheral muscarinic synapses are involved, nor does it provide a more detailed understanding of the area of the brain required for OP-induced apnea.

3.1. Basic central respiratory neuroanatomy

Neurons involved in respiration are concentrated in three distinct locations: dorsal, ventral and pontine respiratory groups. The dorsal respiratory group in the medulla is located in the dorsolateral nucleus tractus soltarius (NTS), which is involved in synaptic transmission of respiratory vagal and glossopharyngeal afferent signals.(Ezure et al., 1991) The ventral group is located in the ventrolateral medulla, and is divided into three regions: caudal, intermediate and rostral. The rostral ventral respiratory group contains the pre-Botzinger complex (preBotC) (Hsieh et al., 1998; Smith et al., 1991) (Schwarzacher et al., 2011). The pontine respiratory group is known as the pneumotactic center and contains the nucleus parabrachialis medialis and the Koliker-Fuse nucleus (Kubin et al., 2006; Mulkey et al., 2004). Other neurons involved in respiration are located throughout the brain and provide afferent input during respiration (see Fig. 1).

Many of the areas involved in central respiratory control contain cholinergic synapses. Cholinergic neurons are located within several structures throughout the CNS and PNS and are thought to serve different functional roles in the control of respiration. The preBotC in the rostral ventral respiratory group contains cholinergic neurons and is considered to be essential in generation of central respiratory activity (Mulkey et al., 2004; Schwarzacher et al., 2011; Shao and Feldman, 2000). The pontine respiratory group in the pons contains cholinergic circuits and assists in switching from inspiration to expiration (Dutschmann and Dick, 2012). In addition, cholinergic neurons on the ventral surface of the medulla are involved in CO_2 chemosensitivity (Bruce and Cherniack, 1987; Nattie et al., 1989; Putnam et al., 2004). Peripheral cholinergic receptors in the carotid bodies are involved in responses to changes in oxygenation (Dinger et al., 1991). Pulmonary mechanoreceptors and peripheral muscle mechanoreceptors provide input to the brainstem via cholinergic pathways (Kubin et al., 2006). For example, slowly adapting stretch receptors in the lung provide afferent