

MEETING ABSTRACTS

RESPIRATION DURING ORGANOPHOSPHATE AND CARBAMATE INTOXICATION WHEN ACETYLCHOLINESTERASE IS NOT ANCHORED AT CHOLINERGIC SYNAPSES

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Intoxications with organophosphate or carbamate shut down control of breathing in minutes. These central apneas are reversed by atropine the well-known antidote of acetylcholinesterase (AChE) inhibitors. But how the excess of ACh triggers the crisis remains unclear. If the buildup of ACh on the post-synaptic receptors at cholinergic synapses is critical, we expected that mice in which the synaptic transmission is adapted to the deficit of AChE should resist to intoxication with carbamates. AChE is specifically anchored in the synapses by ColQ at the neuromuscular junction (NMJ) and by PRiMA in central nervous system (CNS). We have thus intoxicated mice with paraoxon, physostigmine or pyridostigmine and recorded in great details the modifications of breathing in double chamber plethysmography. Physostigmine triggers very long end inspiration pauses (EIP) in WT whereas pyridostigmine provokes only short EIP. The duration of EIP was changed with physostigmine or pyridostigmine in PRiMA KO mice when the brain was adapted to a huge excess of ACh. Surprisingly, when AChE is absent at the NMJ, EIP were much shorter with physostigmine. If AChE in the respiratory center is a key target, we expected long EIP when AChE is normal in the brain and reduced in muscles. Altogether these observations do not support that the change of the synaptic transmission explains the central shutdown control of breathing when cholinesterases are inhibited. In addition, we observed that methacholine provokes similar alteration of breathing when injected subcutaneously to mice. I will discuss a novel model to reconcile these observations.