Title: THE PREJUNCTIONAL EFFECTS OF NON-DEPOLARIZING MUSCLE RELAXANTS IN THE CAT

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Introduction. Atracurium and vecuronium, non-depolarizing neuromuscular blocking agents of intermediate duration of action, have been recently shown to have prejunctional effects at the cat soleus neuromuscular junction[1,2]. This study investigated the effects of the long acting non-depolarizing neuromuscular blocking agents, d-tubocurarine and pancuronium, and the nicotinic non-depolarizing ganglionic blocker, hexamethonium (C6) at the cat soleus motor nerve ending to determine if these agents had similar prejunctional effects.

Methods. The technique developed by Standaert was employed to study the effect of pancuronium, d-tubocurarine and C6 on the repetitive activity generated at the cat soleus motor nerve endings. This activity, known as post-tetanic repetition (PTR), causes an obligatory potentiation of the indirectly evoked muscle contractile responses known as post-tetanic potentiation or (PTP)[3]. An in vivo soleus nerve-muscle preparation was made in cats anesthetized with alpha-chloralose. The isometric contractile responses of the soleus muscle were recorded on a Grass polygraph via a Grass FT10 force transducer. A dorsal laminectomy was performed exposing ventral roots L6, L7 and S1. The roots containing the motor axons of the soleus nerve were identified and divided into filaments containing one to three soleus axons. The soleus nerve was continuously and supramaximally stimulated at 0.4 Hz except when interrupted for 10 sec tetanic trains of 400 Hz. After this high frequency conditioning, the rate of stimulation was returned to 0.4 Hz and PTR was recorded antidromically from the previously identified soleus axons in the ventral root filaments. The effect of each blocking drug on the motor nerve endings was studied by determining, before and after its administration, both the percentage of motor axons demonstrating PTR and the obligatory PTP. The three agents studied were administered in single intravenous doses.

Results. Pancuronium 5-20 ug/kg, d-tubocurarine 10-20 ug/kg and C6 500-1000 ug/kg suppressed the PTR generated at the cat soleus motor nerve endings in a dose range which did not depress single impulse transmission. The suppression of PTP corresponded with the suppression of PTR. Those pancuronium and d-tubocurarine doses which completely suppressed PTP were threshold doses for blocking single impulse transmission. The C6 did not block neuromuscular transmission. The peak loss of PTR and PTP occurred within 20 min after injection with recovery of both PTR and PTP beginning in approximately 120 min. In some cats, recovery from a partial block of single impulse transmission by larger doses of d-tubocurarine and pancuronium was followed by a potentiation of the muscle contractile response (twitch tension) above the pre-drug control (range 3-20%). Further studies showed that threshold doses of each of the three drugs for the suppression of PTR produced a small potentiation of the muscle responses: d-tubocurarine 10 ug/kg, pancuronium 5 ug/kg, and C6 500 ug/kg. This potentiation was due to a drug-induced neural repetitive activity which was observed in ventral soleus axons. The incidence of the drug-induced repetition ranged from 3% to 17%, depending upon the drug and dose studied.

Discussion. Standaert [3] and Werner [4] have demonstrated that in the cat, tetanic frequency induced and drug-induced neural activity originate at motor nerve endings. Thus, PTR signals a prejunctional event. This study has shown that pancuronium and d-tubocurarine suppress frequency-induced PTR and possess the ability to evoke a drug-induced neural repetition. Previous studies have shown that both atracurium and vecuronium also suppress frequency-induced PTR and have the capacity to evoke a drug-induced neural repetition. These data clearly establish that, as a class of drug, non-depolarizing muscle relaxants have direct prejunctional sites of action. The doses of non-depolarizing muscle relaxants which suppress PTR and PTP, and induce neural repetition are smaller than those which block single impulse transmission. Thus, it follows that at the neuromuscular blocking doses, these muscle relaxants have both prejunctional and postjunctional sites of action. It should be noted that C6 acts only at the prejunctional receptors. Thus, the C6 data suggest that the prejunctional receptor responsible for the PTR suppression and the drug-induced neural repetitive firing is a nicotinic receptor that differs from the postjunctional nicotinic receptor.

References.

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