TITLE: CONTINUOUS INFUSION OF D-TUBOCURARINE INDUCES TOLERANCE AND INCREASES IN NICOTINIC ACETYLCHOLINE RECEPTORS

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This study tested the hypothesis that chronic, subparalytic, competitive antagonism of the neuromuscular junction by d-tubocurarine (dTC) results in proliferation of nicotinic acetylcholine receptors (nAChR) and tolerance to dTC.

After institutional approval, male Sprague-Dawley rats were infused with saline (n=8, controls) or dTC (n=8, experimental group) via a subcutaneous osmotic pump. The experimental group received dTC at a rate of 0.012 $mg \cdot kg.^{-1}hr^{-1}$. Preliminary experiments revealed that this dose of dTC does not result in immobility or paralysis, conditions which may independently increase nAChR associated with tolerance to competitive antagonists.[1] After a two week infusion of saline or dTC the animals were re-anesthetized and a blood sample withdrawn for measurement of base line plasma dTC concentrations. Subsequently the effective doses of dTC for gastrocnemius twitch suppression were determined by the incremental intravenous dose technique. During spontaneous recovery of twitch an intravenous infusion of dTC maintained twitch suppression at 72-74% of control twitch height for 15 mins. at which time a blood sample was obtained for determination of dTC level. Plasma dTC concentrations were assayed by HPLC and nAChR in the gastrocnemius and diaphragm quantitated by ^{125}I-α—bungarotoxin. One way ANOVA was used to test differences between groups with $p < 0.05$ considered significant.

There were no differences between groups in weight gain or observed level of activity. The baseline plasma dTC concentration in the experimental group was (mean ± SE) 0.41 ± 0.07 $\mu g \cdot ml^{-1}$. Despite the presence of the baseline dTC in plasma, the experimental group required the same effective doses of dTC as the controls. The plasma dTC level (mean ± SE) at steady-state 72-74% twitch suppression was significantly higher in the experimental group (0.83 ± 0.04 vs 0.50 ± 0.15 $\mu g \cdot ml^{-1}$) as were the gastrocnemius extrajunctional nAChR (mean ± SE) (19.7 ± 1.8 vs 13.4 ± 1.8 $fmol \cdot mg\ protein^{-1}$). The gastrocnemius junctional and diaphragmatic nAChR were not different.

This study confirms the hypothesis that chronic, competitive anatagonism of the neuromuscular junction induces a proliferation of nAChR and tolerance to the competitive antagonist even in the presence of preserved muscle activity. The higher margin of safety for the diaphragm compared to peripheral muscles relative to receptor occupancy may account for the lack of change in nAChR in the diaphragm.

1. Gronert GA: Anesthesiology 55:547-559, 1981