Local and Systemic Blood Flow Changes Contribute to the Prolongation of Tetrodotoxin Nerve Blocks by Epinephrine.

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Introduction: Epinephrine (E) prolongs bupivacaine nerve blocks in animals and humans by at most 1.5-2-fold. Epinephrine also produces only modest changes in regional blood flow (RBF) in rat sciatic nerve and surrounding muscles(1). Tetrodotoxin (TTX) is a naturally occurring biotoxin that may have future utility for prolonged-duration local anesthesia . Co-administration of E with TTX prolongs rat sciatic nerve blockade by up to 13-fold relative to TTX alone. In the current study, RBF was measured to examine mechanisms underlying the dramatic block-prolonging actions of E with TTX.

Methods: With ACUC approval, 400-500 gm rats were anesthetized with isoflurane 2.5% in oxygen, tracheostomy was performed and ventilation was controlled to normocarbia. Left ventricular and systemic arterial catheters were placed via carotid and axillary routes, respectively. TTX 0.1 ml, either at 60 or 120 μM , was administered percutaneously for sciatic blockade, with or without E, 1:100,000. Labelled microspheres (-^{146}CE, ^{51}Cr, ^{103}Ru, ^{95}Nb, and ^{46}Sc) were injected into the left ventricle pre, and then 5, 15, 30, and 60 min after sciatic block injections. RBFs were analyzed using repeated measures ANOVA. Post-hoc Bonferroni/Dunn tests comparisons were performed in two ways: (1) At each tissue site (sciatic nerve, peri-sciatic muscle, brain, rectus abdominus), RBFs at repeated time points after nerve injection were compared with the pre-nerve injection baseline RBFs in the same tissue site, and (2) At each time point, RBFs for sciatic nerve and peri-sciatic muscle were compared between the injected (left) side and the corresponding site in the control (right) side. Measurements of arterial blood pressure were compared using repeated measures ANOVA/Bonferroni/Dunn tests. Data points and error bars are expressed as the mean ±SD. The significance level was set at $p<0.05$.

Results: Compared with pre-injection baseline, peri-sciatic muscle RBF on the injected side increased 3.7-fold at 5 minutes post sciatic nerve injection of TTX 60 μM, 0.1 mL (Figure 1 A, $p<0.05$). In contrast to findings in peri-sciatic muscle, TTX did not significantly alter sciatic nerve RBF (Figure 1 B). Co-injection of epinephrine 55 μM with TTX 60 μM, 0.1 mL prevented TTX-induced increases in peri-sciatic muscle RBF (Figure 1 C). At 5 minutes post-injection, mean ipsilateral peri-sciatic muscle RBF in the TTX+E group was less than 1/5 of that seen at 5 minutes post-injection in the TTX-alone group. Co-injection of E did not significantly alter sciatic nerve RBF (Figure 1 D). Co-injection of E with TTX prevented TTX-induced decreases in brain RBF (Figure 2 A,D).

Discussion: The results shown above can be interpreted by compartment models in which E delays initial systemic uptake of TTX from peri-sciatic muscle, thereby increasing initial uptake of TTX into nerve (Figure 3 A). If TTX exits the nerve very slowly, then even though E alters muscle RBF for << 1 hour, TTX intraneural content can remain above minimal blocking concentrations for up to 13-15 hours with E, and for only 70 minutes without E, as observed previously .

Figure 1 RBF in nerve and muscle, After TTX, +/- E

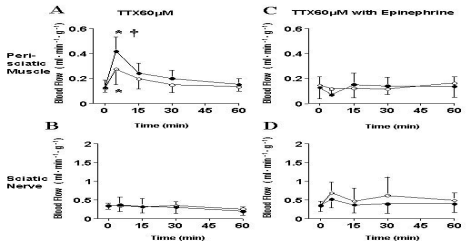


Figure 2 brain and rectus RBF and MAP After TTX, +/- E

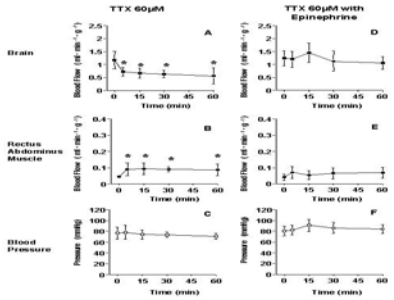
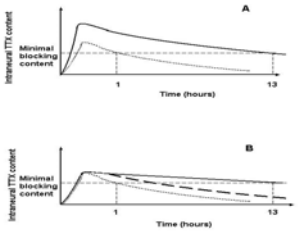


Figure 3 Heuristic models of TTX intraneural content, +/-E



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