High Concentrations of Tranexamic Acid Inhibit Ionotropic Glutamate Receptors

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ABSTRACT

Background: The antifibrinolytic drug tranexamic acid is structurally similar to the amino acid glycine and may cause seizures and myoclonus by acting as a competitive antagonist of glycine receptors. Glycine is an obligatory co-agonist of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. Thus, it is plausible that tranexamic acid inhibits NMDA receptors by acting as a competitive antagonist at the glycine binding site. The aim of this study was to determine whether tranexamic acid inhibits NMDA receptors, as well as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate subtypes of ionotropic glutamate receptors.

Methods: Tranexamic acid modulation of NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and kainate receptors was studied using whole cell voltage-clamp recordings of current from cultured mouse hippocampal neurons.

Results: Tranexamic acid rapidly and reversibly inhibited NMDA receptors (half maximal inhibitory concentration = 241 ± 45 mM, mean ± SD; 95% CI, 200 to 281; n = 5) and shifted the glycine concentration–response curve for NMDA-evoked current to the right. Tranexamic acid also inhibited α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (half maximal inhibitory concentration = 231 ± 91 mM; 95% CI, 148 to 314; n = 5 to 6) and kainate receptors (half maximal inhibitory concentration = 90 ± 24 mM; 95% CI, 68 to 112; n = 5).

Conclusions: Tranexamic acid inhibits NMDA receptors likely by reducing the binding of the co-agonist glycine and also inhibits α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate receptors. Receptor blockade occurs at high millimolar concentrations of tranexamic acid, similar to the concentrations that occur after topical application to peripheral tissues. Glutamate receptors in tissues including bone, heart, and nerves play various physiologic roles, and tranexamic acid inhibition of these receptors may contribute to adverse drug effects. (Anesthesiology 2017; 127:89-97)

TRANEXAMIC ACID (TXA) is an antifibrinolytic drug that is used widely to reduce blood loss resulting from a variety of hemorrhagic causes, including trauma, postpartum hemorrhage, and surgical procedures.1–8 TXA is a synthetic analog of the endogenous amino acid lysine, which binds to the lysine binding site of plasminogen.9 TXA blocks the conversion of plasminogen to plasmin and the degradation of fibrin blood clots, thereby producing hemostatic effects.9

TXA is administered either systemically or topically. Systemic administration to patients by intravenous injection produces concentrations in the cerebrospinal fluid of 30 to 200 μM and plasma of 0.6 to 2 mM.7,10–14 In contrast, topical application of TXA directly to peripheral tissues during some surgical procedures would produce high localized concentrations (0.7 to 100 mg/ml, equivalent to 5 to 600 mM).2 Topical application of TXA is becoming increasingly popular, as this method may reduce bleeding and produce fewer side effects than systemic administration.2 Plasma concentrations after topical application generally are less than one tenth of the level after intravenous administration.2,15–17 TXA inhibition of receptors other than plasminogen may cause adverse effects including seizures and myoclonus.14,18,19 TXA is structurally similar to the inhibitory
neurotransmitter glycine and acts as a competitive antagonist at glycine receptors.\textsuperscript{14} Concentrations of TXA in the low millimolar range reduce inhibitory neurotransmission (or disinhibition), which causes network hyperexcitability and seizure-like events in animal models.\textsuperscript{14,19–21}

The effects of TXA on the major subtypes of excitatory ionotropic glutamate receptors that also modify brain network excitability have not been elucidated fully. These receptor subtypes include \textit{N}-methyl-	extit{D}-aspartate (NMDA) receptors, \textit{\alpha}-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and kainate receptors.\textsuperscript{22} TXA modulation of NMDA receptors is of particular interest because these receptors contain a high-affinity glycine binding site.\textsuperscript{23} Binding of both glutamate and glycine is required for full activation of the NMDA receptors, and drugs that inhibit glycine binding reduce NMDA receptor function.\textsuperscript{24} TXA could compete with glycine at the glycine binding of the NMDA receptor and thereby reduce receptor function. Others have shown that TXA, at low concentrations (1 to 5 mM), does not inhibit excitatory synaptic currents in amygdala slices.\textsuperscript{25} However, the effects of high concentrations of TXA on glutamate receptors, such as those that occur during topical application, have not been elucidated. Glutamate receptors are expressed widely in peripheral tissues, including bone, heart, pancreas, and nerves, where they serve diverse physiologic roles.\textsuperscript{26–32} Thus, it is of interest to determine whether TXA blocks ionotropic glutamate receptors.

For these proof-of-concept studies, currents generated by NMDA, AMPA, and kainate receptors were recorded from hippocampal neurons. The rationale is that these cells express high levels of ionotropic glutamate receptors,\textsuperscript{33} and receptors in hippocampal neurons and peripheral tissues have similar structural, physiologic, and pharmacologic properties.\textsuperscript{26,28,31} The results show that TXA reduces NMDA receptor function by acting as a competitive antagonist at the glycine binding site. Surprisingly, TXA also inhibits AMPA and kainate receptors. These results predict that TXA at high concentrations, applied topically to peripheral tissues, inhibits ionotropic glutamate receptors.

\section*{Materials and Methods}

\subsection*{Cell Culture}

All experimental procedures were approved by the Animal Care Committee of the University of Toronto (Toronto, Ontario, Canada). Primary cultures of hippocampal neurons were prepared from Swiss White mice (Charles River, Canada) as previously described.\textsuperscript{34} In brief, fetal pups (embryonic day 18) were removed from maternal mice that had been euthanized by cervical dislocation. The hippocampi of each fetus were collected and placed on an ice-cooled culture dish. Neurons were then dissociated by mechanical trituration with a Pasteur pipette (tip diameter 150 to 200 \textmu m) and plated on 35-mm culture dishes. The culture dishes were coated with collagen or poly-\textit{d}-lysine (Sigma-Aldrich, Canada). The density of neurons per culture dish was approximately 1 x 10\textsuperscript{6} cells. Two hours later, the medium was changed to a neurobasal medium supplemented with 2% B27 and 1% GlutaMAX (Life Technologies, USA). The medium was changed every 3 days. The low-density dissociated neurons were maintained in culture for 14 to 20 days before use. At this point in time, hippocampal neurons become appropriately polarized, develop extensive axonal and dendritic arbors, and form numerous, functional synaptic connections with one another, which resemble mature hippocampal neurons \textit{in vivo}.\textsuperscript{35} Culture dishes were prepared from at least two different mice for each experiment, and a maximum of two cells was recorded from each dish.

\subsection*{Whole Cell Voltage-clamp Recordings}

Whole cell currents were recorded under voltage-clamp (–60 mV) conditions with an Axopatch 1D amplifier (Molecular Devices, USA) controlled with pClamp 8.0 software (Molecular Devices) via a Digidata 1322A interface (Molecular Devices). Patch pipettes with open-tip resistances of 2 to 3 M\textOmega were pulled from thin-walled borosilicate glass capillary tubes. Patch electrodes were filled with an intracellular solution containing (in mM) 140 cesium chloride, 10 HEPES, 11 EGTA, 2 magnesium chloride, 1 calcium chloride, 4 magnesium adenosine triphosphate, and 2 triethanolamine (adjusted to pH 7.3 with cesium hydroxide and to 285 to 295 mOsm with water). To record NMDA-evoked current, magnesium-free extracellular solution was used and contained (in mM) 140 sodium chloride, 1.3 calcium chloride, 2 potassium chloride, 25 HEPES, and 28 glucose (adjusted to pH 7.4 with sodium hydroxide and to 320 to 330 mOsm with water). To record AMPA- and kainate-evoked current, magnesium chloride (1 mM) was added to the extracellular solution. Tetrodotoxin (300 nM) was added to the extracellular solution to block voltage-sensitive sodium channels. A computer-controlled, multibarreled perfusion system (SF-77B; Warner Instruments, USA) was used to apply the extracellular solution to neurons. The time interval between applications of agonists, including NMDA, AMPA, and kainate, was 2 min. This interval was sufficient to allow receptors to recover from desensitization. No randomization methods were applied. Currents were recorded before and during the application of TXA, and the experimenters were not blinded to the drug application conditions.

\subsection*{Drugs}

TXA, NMDA, AMPA, kainate, and glycine were obtained from Sigma-Aldrich. Tetrodotoxin was purchased from Alomone Labs (Israel). Stock solutions of these reagents were prepared with distilled water.

\subsection*{Data Analysis}

Currents were analyzed with pClamp 10 software (Molecular Devices). The concentration–response plots were fitted to the modified Michaelis–Menten equation: \( I = I_{\text{max}}/[1 + (EC_{50}/c)^{n}] \), where \( I \) is the current amplitude, \( EC_{50} \) is the concentration of agonist that produces currents with 50%
of the maximal amplitude, \( c \) is the concentration of agonist, and \( n_H \) is the estimated Hill coefficient. The concentration–response plots for TXA inhibition were fitted to the following equation: 
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I = \frac{I_{\text{C50}}}{[c^{n_H} + I_{\text{C50}}^{n_H}]},
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where \( I_{\text{C50}} \) is the concentration of TXA that inhibited 50% of the current amplitude.

**Statistical Analyses**

No statistical power calculation was conducted before the study, and the sample size was based on our previous experience with this experimental design. There were no missing data from the results presented in this manuscript. Results are presented as mean ± SD together with 95% CI of the mean. Statistical analysis was performed with GraphPad Prism 5 software (GraphPad Software Inc., USA). Differences between groups were determined with the Student’s \( t \) test or a one-way ANOVA with a Dunnett multiple-comparison post hoc test. A two-tailed hypothesis test was used, and any \( P \) value less than 0.05 was considered significant.

**Results**

**High Concentrations of TXA Inhibit NMDA Receptors**

We first identified the concentration of NMDA that evoked 50% of the maximal current (EC\(_{50}\)) in hippocampal neurons as this information was used to design studies that examined TXA inhibition of NMDA receptors. Application of NMDA (3 to 3,000 μM) rapidly activated inward current, which increased in amplitude with increasing concentrations of NMDA in the presence of glycine (1 μM). The concentration–response plot for NMDA-evoked current revealed an EC\(_{50}\) value of 98 ± 44 μM (95% CI, 51 to 146; \( n = 4 \); fig. 1A).

Next, to study the inhibitory effects of TXA on NMDA receptors, NMDA was applied at a concentration close to the EC\(_{50}\) value (100 μM) together with glycine (1 μM), in the absence or presence of TXA. Low concentrations of TXA (1 mM, 3 mM) had no effect on the amplitude of the peak current. However, higher TXA concentrations (10 mM or greater) rapidly and reversibly inhibited the NMDA-evoked current (fig. 1B). TXA at the threshold concentration (10 mM) inhibited the NMDA current by 4.2 ± 5.4% (95% CI, −0.5 to 8.9; \( n = 5 \)), and the maximum inhibition at 3 M was 97.1 ± 1.8% (95% CI, 95.5 to 98.7; \( n = 5 \)). The concentration–response plot showed that the concentration of TXA required to inhibit 50% of the maximal peak current (IC\(_{50}\)) was 241 ± 45 mM (95% CI, 200 to 281; \( n = 5 \)).

**TXA Is a Competitive Antagonist at the Glycine Binding Site**

To further probe the hypothesis that TXA decreases NMDA receptor function by competitively inhibiting glycine binding, we next examined the inhibitory effects of TXA (100 mM) on current evoked by NMDA (100 μM) with different concentrations of glycine in the extracellular solution. The extent of TXA-mediated inhibition decreased with increasing concentrations of glycine (fig. 2A), and a near-saturating concentration of glycine almost completely abolished TXA inhibition of NMDA-evoked current. Specifically, TXA inhibited NMDA currents by 59.1 ± 23.2%...
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(95% CI, 43.0 to 75.2; n = 8) in the presence of 0.3 μM glycine but by only 2.2 ± 3.7% (95% CI, -0.4 to 4.8; n = 8) when the glycine concentration was increased to 30 μM. We next constructed glycine (0.03 to 100 μM) concentration–response plots for NMDA current, recorded in the absence and presence of TXA (fig. 2B). TXA shifted the glycine concentration–response curve to the right without changing the maximum response. The glycine EC₅₀ increased from 0.48 ± 0.09 μM (95% CI, 0.43 to 0.53; n = 10) to 0.95 ± 0.19 μM (95% CI, 0.81 to 1.1; n = 8) in the presence of TXA (P = 0.02), whereas the Hill coefficient was unchanged (control 1.5 ± 0.6; 95% CI, 1.1 to 1.9; n = 10 vs. TXA 1.6 ± 0.3; 95% CI, 1.5 to 1.7; n = 8, P = 0.9). These results are consistent with the hypothesis that TXA inhibits NMDA receptors by acting as a competitive antagonist at the glycine binding site.

The binding sites of NMDA and glycine interact allosterically such that glycine affinity increases with the binding of NMDA and, conversely, NMDA affinity increases with the binding of glycine. These allosteric interactions predict that TXA blockade should decrease with increasing concentrations of NMDA (because of increased glycine binding). To test this prediction, the inhibitory effects of TXA (100 mM) on NMDA currents were studied under conditions in which the concentration of NMDA was varied whereas the concentration of glycine (1 μM) was fixed (fig. 3). For NMDA 1, 10, and 100 μM, TXA inhibited the currents by 66.1 ± 10.3% (95% CI, 57.9 to 74.3), 48.3 ± 12.7% (95% CI, 38.1 to 58.5), and 26.4 ± 2.5% (95% CI, 24.6 to 28.6), respectively (n = 6). As predicted, TXA inhibition decreased with increasing concentrations of NMDA.

**Inhibition by TXA Is Not Use Dependent or Voltage Dependent**

TXA inhibition should exhibit no use or voltage dependence if it acts as a competitive antagonist at the glycine binding site, rather than as a noncompetitive blocker of the open channel pore. The extent of TXA (100 mM) inhibition was similar after repeated application of NMDA and TXA (fig. 4A), suggesting the block is not use dependent. Next, the concentration of TXA in the extracellular solution was increased to 300 mM (close to IC₅₀ value). Neurons were perfused continuously with this solution. Three sequential applications of NMDA (100 μM) showed that inhibition of three current

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**Fig. 2.** Tranexamic acid (TXA) inhibition of N-methyl-D-aspartate (NMDA)-evoked currents decreases with increased glycine concentration. (A) Representative traces demonstrating decreased TXA (100 mM) inhibition of currents evoked by NMDA (100 μM) with an increased glycine concentration. (B) Glycine concentration–response plots for currents evoked by NMDA (100 μM) in the absence and presence of TXA. Glycine half maximal effective concentration was increased from 0.48 ± 0.09 μM (95% CI, 0.43 to 0.53) without TXA to 0.95 ± 0.19 μM (95% CI, 0.81 to 1.1) with TXA (P = 0.02, unpaired one-tailed Student’s t test). All responses were normalized to the peak current evoked by NMDA (100 μM) and glycine (1 μM) without TXA. The sample sizes in the absence and presence of TXA were n = 10 and n = 8, respectively. All data are presented as mean ± SD.

**Fig. 3.** Tranexamic acid (TXA) inhibition of N-methyl-D-aspartate (NMDA)-evoked currents is reduced with increasing NMDA concentrations. (A) Representative traces showing decreased effects of TXA (100 mM) on currents evoked by an increased concentration of NMDA. (B) Summarized data for the responses shown in (A) (n = 6). Glycine (1 μM) was present continuously in the bath. *P < 0.05, **P < 0.01, ***P < 0.001, one-way ANOVA with Dunnett multiple-comparison post hoc test. All data are presented as mean ± SD.
pulses by TXA was similar (78.9 ± 10.3% with 95% CI, 69.9 to 87.9; 78.5 ± 9.6% with 95% CI, 70.1 to 86.9; and 79.8 ± 9.8% with 95% CI, 71.2 to 88.4; respectively, n = 5; P = 0.5, one-way ANOVA). These results further indicate that TXA inhibition of NMDA receptors was not use dependent. To determine whether TXA-mediated inhibition was voltage dependent, NMDA currents were recorded at different holding potentials in the absence or presence of TXA (100 mM) and current–voltage plots were constructed. TXA decreased the slope of the current–voltage plot but did not change the reversal potential (NMDA: –5.2 mV, +TXA: –5.5 mV, P = 0.9; fig. 4B). Moreover, the extent of TXA-induced inhibition of NMDA currents was equivalent at holding potentials between –60 and +60 mV (P = 0.8, fig. 4C). Thus, TXA inhibition of NMDA currents was not voltage dependent.

High Concentrations of TXA Inhibit AMPA and Kainate Receptors

Unlike NMDA receptors, AMPA receptors and kainate receptors do not require the binding of the co-agonist glycine to promote channel opening. Thus, we hypothesized that TXA would not inhibit AMPA and kainate receptor function. To test this hypothesis, AMPA and kainate were first applied to the neurons to determine EC50 values (fig. 5, A and B). Next, the inhibitory effects of TXA on currents evoked by AMPA (10 μM) and kainate (20 μM), applied at concentrations close to the EC50 values, were studied. Contrary to what was predicted, TXA caused concentration-dependent inhibition of both AMPA- and kainate-evoked currents, with IC50 values of 231 ± 91 mM (95% CI, 148 to 314; n = 5 to 6; fig. 5C) and 90 ± 24 mM (95% CI, 68 to 112; n = 5; fig. 5D), respectively. TXA blockade was rapid and was completely reversed after drug washout.

Discussion

The results show that TXA inhibited ionotropic glutamate receptors, but only at high millimolar concentrations. The efficacy of TXA inhibition of NMDA receptors depended on the concentrations of glycine and NMDA, and the blockade was neither use dependent nor voltage dependent. TXA also
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Inhibited AMPA and kainate receptors at concentrations that are similar to those that inhibited NMDA receptors.

These results build on two previous studies that examined the effects of TXA on glutamate receptor function.18,25 In one of these studies, electrophysiologic recordings showed that TXA did not inhibit excitatory currents in amygdala slices, but only low millimolar concentrations were studied.25 More specifically, TXA concentrations less than 10 mM did not modify synaptic currents generated by glutamate receptors.25 These findings are consistent with our results. In the second study, TXA, at concentrations up to 10 mM, did not bind to NMDA receptors in rat cortical tissue.18 However, the experimental conditions used in the study did not favor TXA binding as the extracellular solution contained high concentrations of NMDA and glycine. TXA blockade of NMDA receptors is reduced under these conditions, possibly because of a competitive interaction between glycine and TXA at the NMDA receptor.

The results from our electrophysiologic studies do not discern whether TXA binds directly to NMDA receptors or indirectly reduces receptor function. However, several lines of evidence suggest that TXA inhibits NMDA receptors directly by preventing glycine from acting as a full co-agonist at these receptors. First,

Fig. 5. Tranexamic acid (TXA) inhibits α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)- and kainate-evoked currents. (A and B) Representative traces and the concentration–response plots for currents evoked by (A) AMPA and (B) kainate. The half maximal effective concentration was 8.6 ± 4.0 µM (95% CI, 5.2 to 12.0) for AMPA responses and 21.8 ± 3.6 µM (95% CI, 18.3 to 25.3) for kainate responses. The sample sizes for 0.3 to 10, 30 to 100, and 300 µM AMPA were n = 6, n = 5, and n = 4, respectively. The sample size for kainate was n = 4. (C and D) Representative traces and the corresponding concentration–response plots demonstrating the inhibitory effects of TXA on currents induced by AMPA (10 µM, C) and kainate (20 µM, D). The sample sizes for 3 to 100 mM and 300 to 3,000 mM TXA on AMPA currents were n = 6 and n = 5, respectively. The sample sizes for TXA on kainate currents were n = 5. All data are presented as mean ± SD.
high extracellular concentrations of glycine reduce TXA blockade. Second, TXA shifts the glycine concentration–response plot to the right without reducing the maximal NMDA-evoked current response. Third, TXA inhibition of NMDA receptors is not use dependent or voltage dependent, which suggests that TXA lacks the features of steric blockers, such as magnesium and ketamine, which occlude the open channel pore.39–41

Interestingly, increasing the concentration of NMDA reduced TXA inhibition of NMDA receptors. This result is consistent with evidence indicating that glutamate and glycine binding to the NMDA receptors is allosterically coupled.36,37 Glutamate agonists increase [3H]glycine binding, whereas glutamate antagonists decrease [3H]glycine binding.37 Reciprocally, competitive antagonists at the glycine binding site allosterically reduce glutamate binding.36 Increasing the concentration of NMDA likely increases glycine affinity, thereby reducing TXA inhibition.

TXA also inhibits AMPA receptors and kainate receptors. These results were unexpected, given that the AMPA and kainate receptors lack a glycine binding site.22 However, TXA inhibits other transmitter-gated ion channels that lack a glycine binding site, including γ-aminobutyric acid type A receptors.14,18,25 It remains unknown how TXA inhibits AMPA and kainate receptors, and further studies are required to determine whether inhibition results from steric, allosteric, or other indirect mechanisms.

Although we examined the TXA sensitivity of glutamate receptors expressed in central neurons, the receptors expressed in peripheral tissues are more likely to be exposed to high millimolar concentrations of TXA. Nevertheless, ionotropic glutamate receptors in peripheral tissues and central neurons exhibit similar structural, kinetic, and pharmacologic properties, suggesting that the results are clinically relevant.36,28,31 For example, in both central neurons and peripheral tissues, GluN1 and GluN2 subunits form functional NMDA receptors.28,31 Also, current generated by glutamate receptors in bone and heart tissue exhibits kinetic and pharmacologic sensitivities that are similar to those of glutamate receptors in neurons.26,28 For example, NMDA receptors in bone cells and neurons are inhibited by both magnesium ions and the high-affinity antagonist MK-801,26 suggesting that receptors expressed in neurons and nonneuronal tissues likely exhibit similar sensitivity to TXA.

High concentrations of TXA that inhibit glutamate receptors could occur after topical application of the drug. Glutamate receptors expressed in peripheral tissues would be exposed to such high concentrations. For example, topical application of TXA is used commonly during orthopedic surgery.17,42–45 NMDA receptors composed of GluN1 and GluN2A-D are expressed in osteoblasts and osteoclasts in bone.28,31 As such, TXA inhibition of NMDA receptors could alter bone healing. Furthermore, receptor subunits of NMDA (GluN1 and GluN2), AMPA (GluA2 and GluA3), and kainate (GluK1 and GluK2) are expressed in the heart, pancreas, and gastrointestinal tissue.28,30,46 Cardiac glutamate receptors, which are localized preferentially within the conducting system, the nerve terminals, and the intramural ganglia cells,27 are involved in conducting impulses and rhythm control.27,47 It is plausible that topical application of TXA to the heart’s conducting system could cause dysrhythmias. Inhibition of NMDA receptors in human and mouse pancreatic islets increases secretion of insulin, so receptor inhibition by TXA could alter glucose levels.48 Finally, inhibition of NMDA receptors in peripheral nerves alters nociception in both rodents and humans.49

Awareness of such potential “off-target” effects secondary to TXA effects on glutamate receptors will inform studies that seek to identify adverse effects of topically applied TXA in patients. Clinical studies first focused on the adverse consequences of antifibrinolytic effects of TXA, including deep vein thrombosis, stroke, and myocardial infarction.50–53 Side effects due to off-target receptor effects only have been recognized recently. For example, seizure and myoclonus likely due to TXA inhibition of glycine receptors and γ-aminobutyric acid type A receptors and mechanistically based treatments for these seizures only have been identified recently.19 By analogy, the physiologic roles of glutamate receptors expressed in peripheral tissues are only beginning to be understood. It will be worthwhile, in future studies, to determine whether TXA inhibition of such physiologic functions contributes to adverse effects of TXA.

In summary, high concentrations of TXA inhibit ionotropic glutamate receptors. These preclinical results will support future studies aiming to clarify the safety and consequences of applying TXA topically to nonneuronal tissues and peripheral nerves in patients.

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Competing Interests
The authors declare no competing interests.

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