Tranexamic acid impairs $\gamma$-aminobutyric acid receptor type A-mediated synaptic transmission in the murine amygdala: a potential mechanism for drug-induced seizures?

Abstract:
Tranexamic acid (TXA) is commonly used to reduce blood loss in cardiac surgery and in trauma patients. High-dose application of TXA is associated with an increased risk of postoperative seizures. The neuronal mechanisms underlying this proconvulsant action of TXA are not fully understood. In this study, the authors investigated the effects of TXA on neuronal excitability and synaptic transmission in the basolateral amygdala. Patch clamp recordings and voltage-sensitive dye imaging were performed in acute murine brain slices. Currents through $\mathrm{N}$-methyl-$\mathrm{D}$-aspartate, $\gamma$-amino-$3$-hydroxy-$5$-methyl-$4$-isoxazolepropionic acid, and $\gamma$-aminobutyric acid receptor type A (GABAA) receptors were recorded. GABAA receptor-mediated currents were evoked upon electrical stimulation or upon photolysis of caged GABA. TXA was applied at different concentrations. Voltage-sensitive dye imaging demonstrates that TXA (1 mM) reversibly enhances propagation of neuronal excitation (mean ± SEM, 129 ± 6% of control; n = 5). TXA at concentrations of 0.1, 0.3, 1, 5, or 10 mM led to a dose-dependent reduction of GABAA receptor-mediated currents in patch clamp recordings. There was no difference in the half-maximal
inhibitory concentration for electrically (0.76 mM) and photolytically (0.84 mM) evoked currents (n = 5 to 9 for each concentration), and TXA did not affect the paired-pulse ratio of GABA receptor-mediated currents. TXA did not impact glutamatergic synaptic transmission. This study clearly demonstrates that TXA enhances neuronal excitation by antagonizing inhibitory GABAergic neurotransmission. The results provide evidence that this effect is mediated via postsynaptic mechanisms. Because GABA receptor antagonists are known to promote epileptiform activity, this effect might explain the proconvulsant action of TXA.

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