

GABAERGIC DRUGS BECOME NEUROTOXIC IN CORTICAL NEURONS PRE-EXPOSED TO BRAIN-DERIVED NEUROTROPHIC FACTOR

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Excitotoxicity contributes to neuronal death in a variety of acute and chronic neurodegenerative disorders. Pharmacological activation of GABA_A receptors, which form ligand-gated Cl⁻ channels, is potentially one of the most powerful neuroprotective strategies because the influx of extracellular Cl⁻ produces membrane hyperpolarization. However, benzodiazepines or barbiturates, have little value as neuroprotective agents in animal models. An interesting possibility is that the effect of GABAergic drugs is context-dependent, i.e. is influenced by environmental factors that regulate the intracellular concentrations of Cl⁻. During early postnatal life, activation of GABA_A receptors induces membrane depolarization by promoting Cl⁻ efflux instead of Cl⁻ influx. This may reflect a reduced expression of the KCC2 neuronal K⁺/Cl⁻ cotransporter. Expression of KCC2 is down-regulated by brain-derived neurotrophic factor (BDNF), which is produced by astrocytes and microglia. BDNF causes a depolarizing shift in the anion reversal potential, which inverts the polarity of GABA currents. BDNF delivery to the brain is considered as a valuable strategy for the treatment of neurodegenerative disorders, such as Parkinson's disease or Huntington's disease. It is important to know how GABAergic drugs affect the viability of neurons exposed to BDNF. We have addressed this issue in cultured neurons undergoing excitotoxic degeneration. A 24-h pretreatment with BDNF (25 ng/ml) enhanced excitotoxic neuronal death in mixed cultures of mouse cortical cells challenged with NMDA. To explore the underlying mechanism(s), we combined NMDA with the GABA_A receptor antagonist, bicuculline, which enhanced NMDA toxicity in control cultures but, unexpectedly, became neuroprotective in cultures pre-treated with BDNF. The same effects were obtained with the GABA_A receptor agonist, muscimol, with the GABA_A receptor positive allosteric modulators, diazepam, lorazepam, and phenobarbital, as well as by drugs that indirectly enhance GABAergic transmission including the GABA uptake inhibitor, SKF 89976A, and the mGlu1 metabotropic glutamate receptor antagonists, LY367385 and CPCCOEt. These data indicated that activation of GABA_A receptors facilitated the neurotoxic activity of NMDA in cultures pretreated with BDNF. This was likely due to changes in the anion reversal potential. These data raise the concern that GABAergic drugs, including barbiturates and benzodiazepines, may exacerbate excitotoxic neuronal death under pathological or pharmacological conditions associated with increases in brain BDNF levels.