Determining the Anticonvulsant Potential of Oral Allopregnanolone
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Abstract:
Allopregnanolone (ALP) is a neurosteroid metabolite of progesterone and potentiates GABA$_A$Cl$^-$ currents with resultant sedative, anticonvulsant, and anxiolytic characteristics. ALP is neuroprotective in many animal models of neurodegenerative conditions. Thus far, studies have only examined its parenteral administration. Given the widespread therapeutic potential of ALP, these experiments sought to evaluate the oral bioavailability of allopregnanolone by examining its ability to protect against pentylenetetrazol (PTZ)-induced seizures. Given sufficient bioavailability, orally administered allopregnanolone was predicted to suppress PTZ-induced seizures in mice in a dose-dependent manner and a lipid, canola oil vehicle was suspected to enhance bioavailability relative to the more aqueous, Tween 80 vehicle. The time point of maximal effect for ALP was determined by oral gavaging male NIH Swiss mice with 250 mg/kg of ALP and sedation scored by assessing relevant behavioral parameters outlined in the Irwin test. Peak sedation of ALP in canola oil occurred 90 minutes post-oral gavage and 45 minutes post-gavage with Tween 80 as the vehicle. In the PTZ seizure challenge, mice were given various doses of ALP in either Tween 80 or canola oil and then at the previously determined time of peak effect, injected with 80 mg/kg PTZ subcutaneously and observed for 30 minutes for seizure protection, defined as the absence of clonic spasms. Mice receiving ALP showed a dose-dependent protection from seizures compared to PBS and vehicle controls and an increased latency to first clonus (p<0.05 using a one-way ANOVA). At 250 mg/kg ALP in canola oil, all mice (N=8) were protected from seizures. A dose response curve was established and ALP in canola oil was significantly more potent, with an ED$_{50}$ of 131.13 mg/kg compared to ALP in Tween 80’s ED$_{50}$ of 221.57 mg/kg. The low oral bioavailability of ALP is likely due to poor aqueous solubility, leading to dissolution-rate limited absorption. The enhanced bioavailability with canola oil may be attributed to facilitation of drug transport across the unstirred water layer by stimulating bile secretion and the formation of micelles or to the enabling of lymphatic transport and its bypass of first pass metabolism in the liver.