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CO-APPLICATION OF THE STEROID ALFAXALON ENHANCES THE GABA_AERGIC EFFECTS OF PROPOFOL AND DIAZEPAM

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The GABA_A receptor modulators propofol and diazepam are in clinical use as anesthetics, anxiolytics and anticonvulsants. However, both drugs, particularly at high doses, cause clinically undesired effects. Propofol can cause irregular heart rate and low blood pressure, while diazepam, like many other benzodiazepines, has long-lasting effects. Thus, it can be clinically advantageous to find ways to administer lower doses of these drugs while still maintaining overall efficacy. One approach is to combine either drug with another GABA_Aergic agent, such as a potentiating neuroactive steroid that by itself has minimal effect. In this study, we looked at the ability of the steroid alfaxalone to amplify GABA_Aergic responses to either propofol or diazepam using three experimental approaches. In the first experiment, we used whole-cell patch clamp to study the effect of combinations of alfaxalone with either propofol or diazepam on decay times of spontaneous inhibitory postsynaptic currents (sIPSCs) in rat hippocampal neurons. Co-application of 300 nM, but not 10 nM, alfaxalone with propofol or diazepam resulted in an enhancement of the decay time constant of sIPSCs. Next, we verified these results on recombinant human $\alpha 1\beta 2\gamma 2L$ GABA_A receptors expressed in *Xenopus* oocytes using two-electrode voltage clamp. We found that exposure to alfaxalone enhanced the ability of propofol or diazepam to potentiate responses to a low concentration of GABA. In the third experiment, we studied the effect of alfaxalone on loss-of-righting induced by propofol or diazepam in *Xenopus* tadpoles. Loss of righting is a proxy for loss of consciousness and mediated by actions on GABA_A receptors. We observed left-shifted dose-response curves during coapplication of alfaxalone with propofol or diazepam. These results demonstrate that coapplication of alfaxalone can result in reduced dosage requirement for propofol and diazepam.