THE INTERACTIONS OF 5-HT1A AGONISTS AND BENZODIAZEPINES IN MODELS OF PHYSICAL DEPENDENCE.

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U-93385E is a high intrinsic activity 5-HT1A agonist with potent antianxiety effects in animal models. In the course of evaluating this compound, we sought to determine whether it shared with the benzodiazepine anxiolytics any similar physical dependence-inducing properties. Not surprisingly, in an acute (3-day dosing) dependence assay which utilizes flumazenil to precipitate abstinence, and in a diazepam cross dependence paradigm, U-93385E was inactive. Other 5-HT1A agonists (8-OH-DPAT, buspirone and ipsapirone) were similarly inactive. However, we found that U-93385E was capable of blocking precipitated abstinence hyperexcitability in diazepam-dependent mice as measured by electroshock seizure thresholds. This observation caused us to more closely investigate the interactions of the 5-HT1A agonists and flumazenil on electroshock-induced seizures. The results revealed that U-93385E, though having little effect on seizure thresholds, raised them when combined with flumazenil. In contrast, both ipsapirone and 8-OH-DPAT raised thresholds. However, the effect of ipsapirone, but not that of 8-OH-DPAT, was blocked by flumazenil. The diversity of these interactions indicates that they are not due strictly to 5-HT1A mechanisms, and that caution must be exercised in the interpretation of the results of physical dependence experiments based on withdrawal hyperexcitability.

Age and Serum Fluphenazine Concentrations

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Fluphenazine (FPZ) is relatively commonly used in geriatric patients. However, the effects of advanced age on FPZ pharmacokinetics are poorly understood. To test the hypothesis that FPZ concentration/dose ratios are positively associated with age, we retrospectively studied 43 patients who were on stable doses of FPZ and had serum concentrations determined by HPLC during their hospitalization. Their ages ranged from 20 yrs to 87 yrs. In 11 patients FPZ concentrations were below the limit of detection. The ages and FPZ doses of patients with detectable FPZ concentrations overlapped those of patients with nondetectable FPZ. In patients with detectable FPZ, the correlation between age and FPZ concentration/dose was not significant (r=.15). In aged patients, lower doses of FPZ may not be generally necessary to achieve concentrations equivalent to those in younger patients.

BINDING OF FELBAMATE TO GLYCINE RECEPTORS IN HUMAN POSTMORTEM BRAIN: ROLE IN MEDIATING ANTICONVULSANT AND NEUROPROTECTANT EFFECTS.

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Activation of receptors for NMDA has been shown to be associated with seizures and ischemic damage in brain. Neuromodulation of NMDA-mediated activity can occur at several sites including strychnine-insensitive glycine receptors (SIGR). Autoradiography reveals that felbamate is capable of interacting with SIGR in human brain. This property is not shared by the other anticonvulsant compounds including carbamazepine, phenytoin, valproic acid and phenobarbital even when present at relatively high concentrations. The results show that felbamate decreases antagonist ([^{3}H]5,7 dichlorokynurenic acid) binding, but increases agonist ([^{3}H]glycine) binding at SIGR. Felbamate is acting as a functional antagonist at subtypes of SIGR, or at an allosterically coupled site on the protein, to modulate NMDA associated channel opening in human brain. This property is related to the effectiveness of the compound as a unique anticonvulsant and neuroprotectant.

INOSITOL MODULATES IN VIVO EFFECTS OF LITHIUM IN RATS

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Lithium inhibits inositol monophosphatase of the phosphoinositide (PI) pathway, an effect which was suggested to be responsible for lithium's therapeutic action (Berridge et al, 1982). Lithium reduced inositol levels in rat brain following some treatment regimens and supplemental inositol reversed some of lithium's effects, including seizures resulting from lithium potentiating the response to cholinergic agonists (Tricklebank et al, 1991; Kofman et al, 1993). We used EEG measurements in rats to determine the effect of inositol on seizures induced by pilocarpine (30 mg/kg, sc) following pretreatment with acute (3 mmol/kg, ip, 20 hrs) or chronic (4 weeks) lithium. Myo-inositol (0-55 mmole, icv) dose-dependently attentuated lithium plus pilocarpine seizures when an acute but not a chronic lithium treatment was used. Epi-inositol, which is not utilized for PI synthesis blocked acute lithium and pilocarpine-induced seizures in 50% of tested rats. Similarly to its effect on muscarinic agonists, lithium increased the response to DOI, a selective 5-HT$_2$/5-TH$_1$C (PI-linked) agonist (Williams and Jope, 1994). While R-(-)DOI (8 mg/kg, ip) alone was not convulsive, lithium plus DOI evoked seizures. In some rats tested, myo-inositol blocked the effect of lithium on DOI-induced seizures.