PRECLINICAL PHARMACODYNAMICS OF ANXIOLYTICS: EFFECTS OF CHRONIC BENZODIAZEPINE ADMINISTRATION

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ABSTRACT

Benzodiazepine anxiolytics act at specific receptors located on the GABA_A receptor complex on post-synaptic neurons. We developed a mouse model to assess pharmacodynamics and neuro-chemical effects during chronic benzodiazepine administration. During chronic lorazepam administration, animals developed behavioral tolerance and benzodiazepine receptor downregulation in several brain regions after 1 week of treatment. Similar results were observed for clonazepam. However, for alprazolam, these alterations occurred more rapidly, after 2-4 days, and neurochemical changes occurred primarily in cortex. In contrast to results with benzodiazepine agonists, chronic antagonist and “inverse agonist” treatment had opposite effects on behavior and were associated with receptor upregulation. After benzodiazepine agonist discontinuation, behavioral and neurochemical effects were also opposite to those observed during chronic administration, suggesting the presence of a “withdrawal” syndrome. Administration of carbamazepine after lorazepam discontinuation attenuated the behavioral and neurochemical withdrawal effects. Studies to determine the cellular mechanisms of these receptor alterations indicated that receptor increases after drug discontinuation were likely to be due to enhanced receptor production. During chronic administration, receptor mRNAs were decreased, but this change occurred after the development of tolerance and receptor downregulation.

Benzodiazepine anxiolytics act at a specific binding site in the central nervous system to exert their pharmacodynamic effects. This site is located on the GABA_A receptor complex on post-synaptic neurons (Olsen and Tobin, 1990). Binding of benzodiazepine agonists enhances GABA binding, which in turn opens a ligand-gated chloride channel producing
neuronal hyperpolarization. Since the introduction of benzodiazepines into clinical practice almost thirty years ago, pharmacodynamic alterations have been reported during chronic administration. In particular, tolerance occurs to most benzodiazepine actions during chronic treatment (Greenblatt and Shader, 1978). Tolerance has been especially problematic in the use of benzodiazepines as anticonvulsants and sedatives. In addition, discontinuation of benzodiazepines after chronic use is associated with the development of “withdrawal” or discontinuation syndromes (Greenblatt et al., 1990). Withdrawal has limited the use of benzodiazepines as anxiolytics and hypnotics.

Behavioral tolerance and a behavioral discontinuation syndrome have been reported in animals exposed to chronic benzodiazepines (Miller, 1991). However, relatively little information has been available concerning the neurochemical substrate of these chronic benzodiazepine effects. To elucidate the basis for pharmacodynamic alterations during chronic benzodiazepine administration, we developed a mouse model of benzodiazepine tolerance and withdrawal. Results of studies in this model are described briefly below.

Initial studies of chronic benzodiazepine administration used lorazepam (Miller et al., 1988a). This compound is intermediate in half-life, potency, and receptor binding and has no active metabolites in the mouse or human. Lorazepam was delivered by subcutaneously implanted osmotic pumps. This method provides continuous serum concentrations analogous to those obtained in humans receiving multiple daily doses of a benzodiazepine, as is common clinically. Using a simple measure of ataxia, mice developed tolerance to lorazepam over a broad dose range (1-10 mg/kg/d) after 7 days of administration. Tolerance persisted to 14 days of administration. Plasma and brain concentrations of lorazepam remained constant during this period. Benzodiazepine receptor binding determined by in vivo uptake of [3H]flumazenil also decreased in several brain regions at day 7 of administration. Binding determined in vitro in cortex exhibited a similar pattern. Finally, GABA_A receptor function was determined by stimulation of chloride uptake into cortical preparations by the GABA analog muscimol. Uptake was decreased after 7 days of lorazepam administration.

These data indicate that downregulation of the benzodiazepine receptor, and decreased function of the GABA_A receptor complex, are temporally associated with the development of tolerance. Similar findings with regard to receptor downregulation have been reported by Tietz and co-workers (1986) using chronic flurazepam, and by Marley and Gallager (1989) using chronic diazepam. Although these results do not establish that neurochemical changes cause behavioral effects, the temporal association suggests a causal role or a common response to another factor.

Subsequently, we have evaluated effects of chronic administration of several other benzodiazepine agonists, alprazolam and clonazepam. Alprazolam is a triazolobenzodiazepine with efficacy in panic disorder as well as anxiety. Some clinical reports suggest that discontinuation syndromes are more common and more severe with alprazolam (Roy-Byrne and Hommer, 1988). Chronic alprazolam administration in mice is associated with behavioral tolerance at 4 days of administration (Miller et al., 1989b). Benzodiazepine receptor binding in vivo and in vitro in cortex is also decreased after 4 days, as is GABA-dependent chloride uptake. Thus, alprazolam appears to be similar to lorazepam except that behavioral and neurochemical alterations occur more rapidly. In addition, effects of alprazolam are largely confined to cortex, whereas lorazepam-induced alterations occur in hippo-