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Effect of nitric oxide synthase inhibitors on benzodiazepine withdrawal in mice and rats

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Abstract:
This study was undertaken to evaluate the effect of nitric oxide (NO) synthase inhibitors on benzodiazepine withdrawal syndrome in mice and rats. Diazepam withdrawal in mice was read out as intensification of the seizures induced by a subthreshold dose of pentetrazole. In rats, the withdrawal syndrome resulting from chronic administration of diazepam, chlordiazepoxide, clonazepam and temazepam was characterized by audiogenic seizures, hypermotility and weight loss. Administration of the non-selective NO synthase inhibitors N^G-nitro-L-arginine (L-NOARG) and N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME) significantly attenuated the withdrawal syndrome (i.e., pentetrazole-induced seizures) in diazepam-dependent mice. L-NOARG significantly suppressed hypermotility in clonazepam-dependent rats and inhibited the decrease in body weight observed after 12 h of withdrawal in chlordiazepoxide- and clonazepam-dependent rats. Moreover, a clear propensity of L-NOARG to protect benzodiazepine-dependent rats against audiogenic seizures was observed. These findings suggest that the cGMP/NO system may participate in causing the signs of benzodiazepine withdrawal.

Key words:
nitric oxide, benzodiazepines, withdrawal, mice, rats