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Biphasic Dose-Response Effect of Baclofen on Haloperidol Catalepsy in the Rat

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RICHARDSON, J. S. AND A. K. RICHARDSON. *Biphasic dose-response effect of baclofen on haloperidol catalepsy in the rat.* PHARMAC. BIOCHEM. BEHAV. 17(4) 855–856, 1982.—Haloperidol-induced catalepsy in rats is reduced by low dose baclofen and is potentiated by high dose baclofen. This biphasic behavioral effect is consistent with reported differences between presynaptic and postsynaptic GABA receptors. Low dose baclofen could have an anti-cholinergic effect by activating presynaptic GABA receptors that inhibit the release of acetylcholine. High dose baclofen could have an anti-dopamine effect by activating postsynaptic GABA receptors that inhibit the firing of dopamine neurons.

Baclofen GABA receptors Haloperidol catalepsy

THE neuroleptic haloperidol produces a cataleptic condition in rats that appears to be a useful animal model of the extrapyramidal motor disorders seen in humans as side effects of neuroleptic therapy. Muscimol, a GABA-mimetic drug, seems to have a biphasic effect on haloperidol catalepsy with low doses antagonizing the catalepsy and high doses potentiating it [6]. Baclofen, the beta-p-chlorophenyl derivative of GABA, readily crosses the blood-brain barrier where it has GABA-mimetic properties. Kaariainen [2] reported that high dose baclofen plus low dose haloperidol produced catalepsy. We now report the biphasic dose dependent actions of baclofen on haloperidol-induced catalepsy that seem to parallel the baclofen-haloperidol interaction observed in a patient [4].

METHOD

Male Sprague-Dawley rats (200–250 g), obtained from Canadian Breeding Labs, were housed in group cages under standard animal colony conditions and were handled daily for at least one week before the experiment. Catalepsy was determined as the length of time that a rat would remain perched spread-eagle (to a maximum of 180 seconds) on 4 wooden pegs (12 mm in diameter) that extended 2.5 cm above a base platform. Laterally the pegs were 8 cm apart and the back and front pegs were 13 cm apart. To minimize the influence of diurnal variations in neural rhythms, all experiments were started at the same time (11:00 a.m.) each day. The rats were given an intraperitoneal injection of 0, 0.1, 1.0, or 10.0 mg/kg baclofen in 1 ml/kg saline. Each rat was tested for catalepsy 2 hours later and then given an IP injection of 0, 0.3, 0.6, or 1.2 mg/kg haloperidol in 1 ml/kg saline. Catalepsy scores were obtained at 30 minute intervals for 2 hours after the haloperidol injection and the 4 determinations were summed to give a Total Catalepsy Score for each rat. The group differences were evaluated statistically by Student's *t*-test.

RESULTS

The effects of the various doses of baclofen on the haloperidol catalepsy dose-response are shown in Fig. 1. Prior to the haloperidol injections, the rats would not perch on the pegs. But during the 2 hours after haloperidol, catalepsy was evident. The Total Catalepsy Score for haloperidol alone increased from a mean of 295 seconds for the 0.3 mg/kg dose, up to 575 seconds for the 1.2 mg/kg dose. The 0.1 mg/kg dose of baclofen had no effect on the catalepsy produced by any dose of haloperidol tested, but the 1.0 mg/kg dose significantly reduced the catalepsy scores of the 0.3 and the 0.6 haloperidol groups. The 10.0 mg/kg dose of baclofen significantly increased the catalepsy scores of the rats receiving 0.6 mg/kg of haloperidol. The near maximal catalepsy produced by the highest dose of haloperidol was not altered by any dose of baclofen tested.

DISCUSSION

Recent neurochemical evidence on the actions of baclofen suggests an explanation for this biphasic effect of baclofen on haloperidol catalepsy. Low dose baclofen (perhaps the (−) isomer) seems to stimulate presynaptic GABA receptors that reduce the release of various excitatory amines [3], including acetylcholine [1]. Thus, low dose baclofen could be acting as an anti-cholinergic agent by inhibiting the release of acetylcholine. This anti-cholinergic effect of baclofen would restore the dopamine-acetylcholine balance in the neostriatum and reduce the extrapyramidal effects of haloperidol just as benztropine does. High doses of baclofen stimulate postsynaptic GABA receptors [5] and inhibit firing in dopa-

mine neurons [2]. Thus high dose baclofen reduces dopamine neurotransmission, magnifies the dopamine blocking effects of haloperidol, and potentiates the extrapyramidal syndrome produced by haloperidol. However, it would appear that the dopamine blocking effects of the highest dose of haloperidol (1.2 mg/kg) used in this experiment were too strong to be modified by either the pre- or postsynaptic actions of baclofen.

This dose dependent biphasic action of baclofen on a dopamine-mediated behavior pattern is consistent with the biphasic effects of other direct acting GABA-mimetic drugs [6]. This behavioral evidence supports the hypothesis that GABA neurons are involved in the extrapyramidal actions of neuroleptics like haloperidol and suggests that there are at least two separate populations of GABA receptors (presynaptic and postsynaptic) that may have exactly opposing effects on brain output functions.

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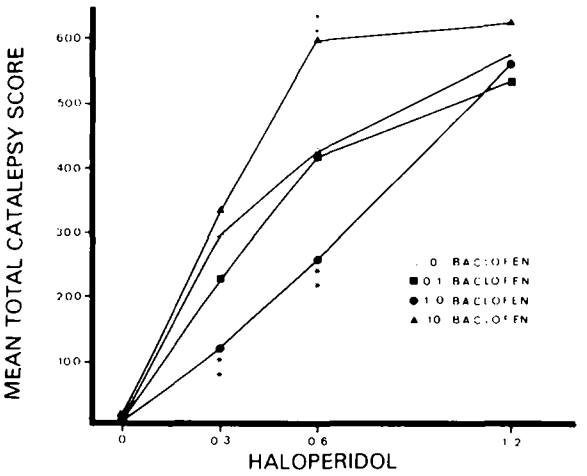

FIG. 1. Dose-response effects of racemic baclofen on catalepsy induced by different doses of haloperidol. Each data point represents the mean Total Catalepsy Score for 5 to 12 rats. Drug doses are mg/kg given intraperitoneally in 1 ml/kg saline. **Indicates p value is less than 0.025.

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