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Selective Blockade of the Discriminative Stimulus Effects of Pentobarbital in Pigeons

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Abstract. The ability of CNS stimulants to block the discriminative effects of pentobarbital was studied in pigeons trained to discriminate IM pentobarbital (5 mg/kg) from saline. Pentobarbital, when administered alone, consistently produced greater than 90% pentobarbital-appropriate responding. The concomitant administration of pentobarbital and increasing doses of bemegride or pentylenetetrazol resulted in a dose-related decrease in pentobarbital-appropriate responses. In contrast, picrotoxin, another CNS stimulant, had little or no effect on pentobarbital-appropriate responding produced by pentobarbital.

Key words: Pentobarbital – Drug discrimination – Antagonism – Bemegride – Pentylenetetrazol – Picrotoxin – Pigeons

The discriminative stimulus effects of pentobarbital in the pigeon have recently been shown to be produced by a number of compounds that produce pentobarbital discriminative effects in other species (Herling et al. 1980). In addition, as has been demonstrated in mammalian species (e. g., Krimmer 1974; Johansson and Jarbe 1975), the pentobarbital discriminative effect is blocked in pigeons by bemegride (Jarbe and Ohlin 1979; Herling et al. 1980). In order to examine further the discriminative stimulus properties of pentobarbital in pigeons and compare them to those found in other species, the central nervous system stimulants bemegride, pentylenetetrazol and picrotoxin were studied in pigeons for their ability to antagonize the discriminative effects of pentobarbital.

Materials and Methods

The subjects were four White Carneaux pigeons maintained at approximately 80% of free-feeding weight. Water and grit were continuously available in each animal's home cage. These pigeons had served as subjects in an earlier pentobarbital discrimination experiment (Herling et al. 1980).

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Experimental sessions were conducted in chambers that have been described previously (Herling et al. 1980). Briefly, the inside front panel of each chamber contained two translucent response keys that were transilluminated during experimental sessions by red 7-W lights. Food (mixed grain) could be presented to the pigeon through a rectangular opening located below the keys.

The training and testing procedures were identical to those described previously (Herling et al. 1980). Each pigeon was required to emit 20 consecutive responses on one of two keys to produce 4-s access to food. The key on which responses produced food was determined by the IM injection of either 5 mg/kg pentobarbital (left key) or saline (right key) administered 5 min before the session. Responses on the inappropriate key reset the response requirement on the appropriate key. Sessions ended after 32 food deliveries or 1 h, whichever occurred first. Training sessions were conducted 6 days per week with pentobarbital and saline injections alternating from one session to the next.

Once the training criteria were met (see Herling et al. 1980), test sessions were conducted with pentobarbital (5 mg/kg), bemegride (0.1, 1, 3, 5.6 or 10 mg/kg), pentylenetetrazol (3, 10, 17.8 or 32 mg/kg) or picrotoxin (0.1, 0.3, 0.6, 1 or 1.8 mg/kg). During test sessions, 20 consecutive responses on either the pentobarbital- or saline-appropriate key resulted in food delivery; in all other respects, test sessions were identical to training sessions. Refer to Herling et al. (1980) for further details of the testing protocol.

All drugs were injected IM, usually in a volume of 1 ml/kg. Test sessions began 5 min after pentobarbital and 10 min after all other drugs. When drug combinations were studied, an injection of bemegride, pentylenetetrazol or picrotoxin was made into the breast muscle on one side of the animal, followed 5 min later by an injection of pentobarbital into the breast muscle on the opposite side.

Drugs. Pentobarbital sodium (Ganes Chemical Works, New York, NY) was dissolved in a solution containing 10% ethanol, 20% propylene glycol, and 70% sterile water. Bemegride (Aldrich Chemical Co., Milwaukee, WI), pentylenetetrazol, and picrotoxin (both from Sigma Chemical Co., St. Louis, MO) were dissolved in sterile water.

Data Analysis. The data for test sessions are presented as the average number of responses throughout the session that were emitted on the pentobarbital-appropriate key, expressed as a percentage of the total responses. The overall rate of respond-

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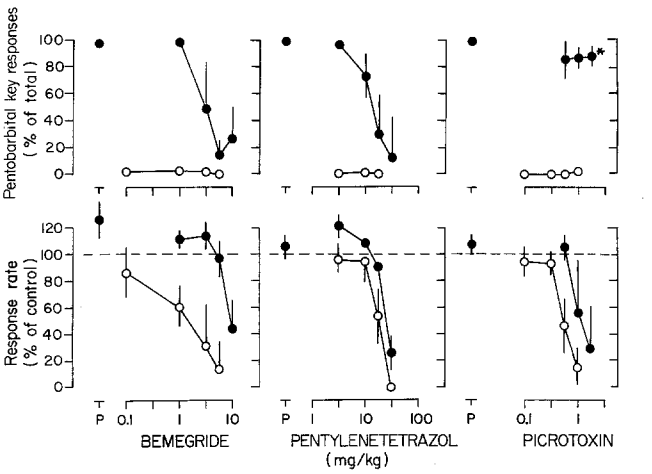

Fig. 1. Effects of bemegride, pentylenetetrazol, or picrotoxin on pentobarbital-appropriate responding produced by 5 mg/kg pentobarbital. Closed circles show the effects of pentobarbital administered alone (indicated at P) or in combination with increasing doses of bemegride, pentylenetetrazol, or picrotoxin. The effects of the stimulants alone are shown by open circles. Upper panel ordinates: percentage of total session responses emitted on the pentobarbital-appropriate key. Lower panel ordinates: rate of responding on both keys, expressed as a percentage of the saline control rates. Abscissae: dose of stimulant, in mg/kg. Each point is the mean of single observations in each of four pigeons, except that pentobarbital-bemegride combinations were studied in only three pigeons. * Only two pigeons responded after the combination of pentobarbital and 1.8 mg/kg picrotoxin. Lines through the points indicate ±1 SEM

ing on the two keys was also recorded during each session. The average rate of responding after drug injection is expressed as a percentage of the previous saline control rates.

Results

Pentobarbital (5 mg/kg) consistently produced greater than 90% pentobarbital-appropriate responding (Fig. 1, upper panels: closed circles above P). When administered alone, bemegride, pentylenetetrazol, and picrotoxin produced little or no drug-appropriate responding (Fig. 1, upper panels: open circles), although each drug produced a dose-related decrease in the rate of responding (Fig. 1, lower panels: open circles). When administered with pentobarbital before the session, both bemegride and pentylenetetrazol produced a dose-related decrease in responses emitted on the pentobarbital key. Bemegride was approximately three times more potent than pentylenetetrazol as an antagonist of pentobarbital (Fig. 1, upper panels) and in decreasing the rate of responding (Fig. 1, lower panels). Picrotoxin, in contrast to bemegride and pentylenetetrazol, had little effect on pentobarbital-appropriate responding produced by pentobarbital (Fig. 1, upper panels). Response rates following combined injections of pentobarbital and either bemegride, pentylenetetrazol, or picrotoxin were generally higher than response rates following injections of the stimulants alone (Fig. 1, lower panels).

Discussion

The discriminative stimulus effects of pentobarbital in the pigeon were blocked by bemegride and pentylenetetrazol, but not by picrotoxin. These results are generally consistent with those reported in both rats (Krimmer 1974) and gerbils (Johansson and Jarbe 1975; Jarbe 1976). Although picrotoxin, in contrast to bemegride and pentylenetetrazol, did not block the discriminative effects of pentobarbital, pentobarbital attenuated the rate-decreasing effects of all three stimulants to some extent.

If rats are trained to discriminate between pentylenetetrazol and saline, bemegride substitutes in 100% of the rats tested, whereas picrotoxin does so in only 60% of the animals (Shearman and Lal 1979, 1980). The relative lack of efficacy of picrotoxin in blocking the discriminative effects of barbiturates or in producing pentylenetetrazol discriminative effects, in contrast to either bemegride or pentylenetetrazol, suggests that bemegride and pentylenetetrazol share a mechanism of action that differs from that of picrotoxin. Although pentylenetetrazol, bemegride, and picrotoxin are central nervous system stimulants, picrotoxin is generally thought to produce its convulsant actions by antagonizing the inhibitory transmitter gamma-aminobutyric acid (GABA), whereas pentylenetetrazol produces convulsant activity by causing permeability changes that result in depolarized neuronal membranes (Franz 1980). Moreover, bemegride and pentylenetetrazol are generally considered to exert very similar pharmacological effects (Hahn 1960). That some of the behavioral effects of pentylenetetrazol are unrelated to GABAergic mechanisms is supported by the finding that a number of GABAmimetics fail to block the discriminative effects of pentylenetetrazol (Shearman and Lal 1980). Since the GABA antagonist picrotoxin does not block barbiturate-discriminative effects in either rodents or pigeons, and various GABAergic drugs (e. g., muscimol, valproate) do not produce pentobarbital-appropriate responding (Herling et al. 1980), the discriminative effects of barbiturates do not appear to be significantly mediated by GABAergic mechanisms. On the other hand, the ability of pentobarbital to reverse the rate-decreasing effects of picrotoxin (Fig. 1) may indicate that this effect of pentobarbital does involve GABAergic mechanisms. This latter observation is consistent with the finding that picrotoxin and various barbiturates inhibit (^{3}H) α-dihydropicrotoxinin binding in rat brain (Ticku 1980), an effect that appears to be related to the ability of these compounds to either inhibit (e. g., picrotoxin) or potentiate (e. g., pentobarbital) GABAergic transmission.

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