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EFFECTS OF ANTIHISTAMINIC DRUGS ON FELINE BRAIN MONOAMINE METABOLISM

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Abstract—Diphenhydramine and phenindamine were administered in various doses to cats and the time course of changes in monoamine metabolite levels in cerebrospinal fluid was determined. Diphenhydramine at a sedative dose did not alter 5-hydroxytryptamine or dopamine metabolism. Excitant doses of diphenhydramine elevated 5-hydroxyindolacetic acid levels, while homovanillic acid levels remained unchanged. At a convulsant dose, diphenhydramine lowered rectal temperature while elevating both 5-hydroxyindolacetic acid and homovanillic acid levels. Phenindamine, which reportedly produces only central nervous system (CNS) excitation and convulsions, caused excitation, tremor and stereotypy, while elevating 5-hydroxyindolacetic acid and homovanillic acid levels in cerebrospinal fluid. These data suggest that antihistaminic-induced sedation is not due to an alteration in brain 5-hydroxytryptamine or dopamine metabolism and that only 5-hydroxytryptamine metabolism is increased during CNS excitation. Stereotypic behavior after phenindamine may occur through a dopaminergic system as reflected by elevated levels of homovanillic acid in cerebrospinal fluid.

Antihistaminic drugs have been shown to produce sedation [1], excitation and tremor, or convulsions [2] depending upon the dose administered. It has been suggested that central monoamines play a role in the production of sedation [3], excitation [4], tremor [5] and convulsions [6]. We hypothesize that antihistamines produce these behavioral states through an alteration in the balance of central monoamine metabolism. To test this hypothesis we have followed the concentrations of 5-hydroxytryptamine and dopamine metabolites in feline cerebrospinal fluid (CSF) for extended periods of time after single injections of drugs. Monoamine metabolite concentrations in the CSF are thought to reflect central monoamine turnover rates of brain amines [7–10].

METHODS

Cats (2.5 to 5.0 kg) were maintained in individual cages with a 12-hr light–12-hr dark schedule. Behavior was observed and rectal temperature was monitored for an 8-hr period during experiments. Cannulae were implanted into the cisterna magna to permit serial collection of CSF [11]. CSF samples of 1.0 ml were collected at 2-hr intervals throughout control and experimental periods, and the major metabolites of 5-hydroxytryptamine (5-HT) and dopamine, 5-hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA), respectively, were assayed fluorometrically [12, 13]. Diphenhydramine hydrochloride (Sigma), dissolved in saline, was administered intraperitoneally in doses producing sedation (0.7 mg/kg), excitation and tremor (10 and 20 mg/kg), and convulsion (30 mg/kg). Phenindamine tartrate (gift from Hoffmann-La Roche), was dissolved in saline, and administered in a dose producing excitation, tremor and stereotypy (10 mg/kg). All doses are expressed in terms of free base. As a control, saline was administered i.p. on the day preceding antihistaminic injection. CSF samples were collected 1-hr prior to injection and at 1-, 3-, 5-, 7- and 24-hr post-injection intervals. Cats were grouped according to drug and dose received, and the individual metabolite levels at each

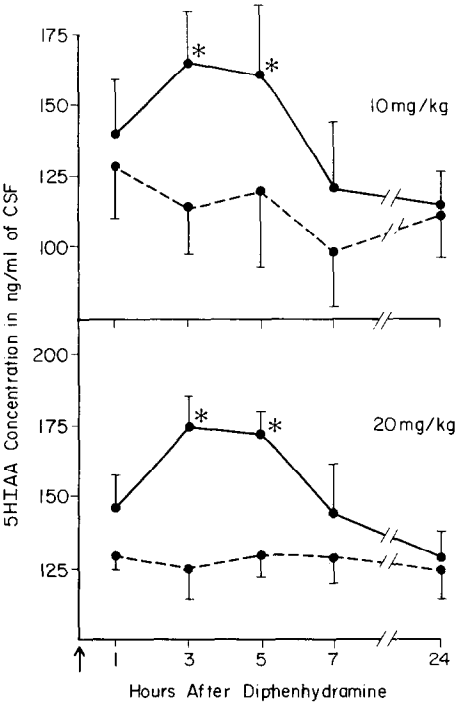

Fig. 1. Effects of diphenhydramine on 5-HIAA concentrations in feline CSF. Solid line (——) represents response to diphenhydramine, dashed line (– – – –), response to saline injection. Each point represents the average of five or six cats ± S. E. Significant differences from control values have been labeled with an asterisk (*) where P is at least less than 0.05. Arrow (↑) indicates time of injection.

time point after the drug were paired with the response to saline in the same animal and analyzed with the paired Student's *t*-test; thus, each animal served as his own control.

RESULTS

Diphenhydramine, administered at 0.7 mg/kg, i.p., produced sedation and EEG synchrony, but no changes from control levels of 5-HIAA or HVA or in rectal temperature. Doses of 10 and 20 mg/kg produced excitation, increased sympathetic nervous system activity, and induced tremor beginning minutes after injection and remaining 4–6 hr after injection, while significantly elevating 5-HIAA levels at 3 and 5 hr post-injection. No change occurred in HVA levels or rectal temperature (Fig. 1). A dose of 30 mg/kg of diphenhydramine produced tonic–clonic convulsions, elevated both 5-HIAA and HVA levels, and decreased rectal temperature 1.5 to 2.5°. Convulsions occurred within 20 min of injection and temperature decrease occurred within 45 min of injection and returned to control within 25 hr (Fig. 2).

Phenindamine at a dose of 10 mg/kg produced excitation, increased sympathetic nervous system activity, and induced tremor (similar to the behaviors and time course seen at 10 and 20 mg/kg of diphenhydramine). It also induced stereotyped behaviors such as repetitive licking or scratching. This dose elevated both 5-HIAA and HVA with no change in rectal temperature (Fig. 3).

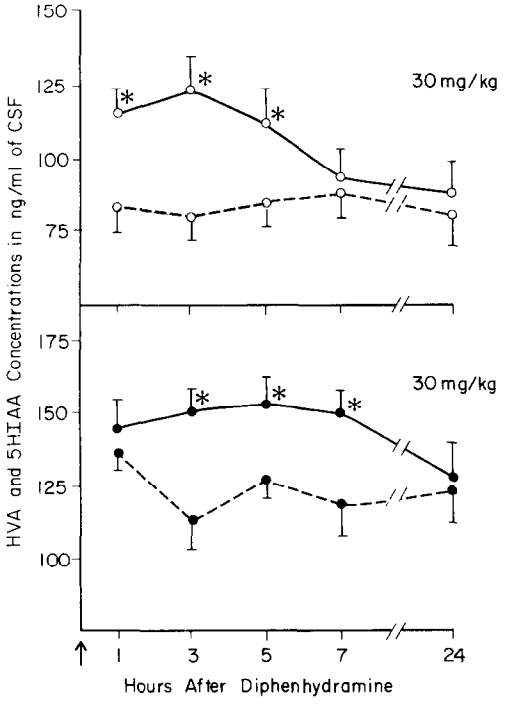

Fig. 2. Effects of diphenhydramine on HVA (○) and 5-HIAA (●) concentrations in feline CSF. Solid line (——) represents response to diphenhydramine; dashed line (– – – –), response to saline injection. Each point represents the average of five or six cats ± S. E. Significant differences from control values have been labeled with an asterisk (*) where P is at least less than 0.05. Arrow (↑) indicates time of injection.

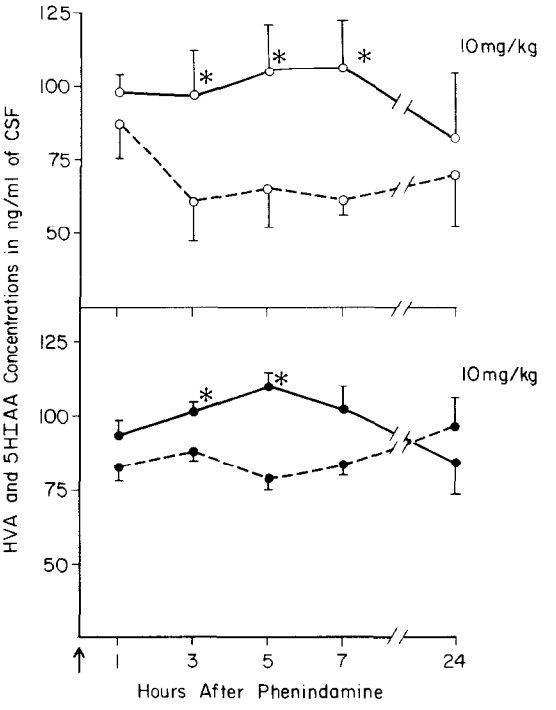

Fig. 3. Effects of phenindamine on HVA (○) and 5-HIAA (●) concentrations in feline CSF. Solid line (——) represents response to phenindamine; dashed line (– – – –), response to saline injection. Each point represents the average of five or six cats ± S. E. Significant differences from control values have been labeled with an asterisk (*) where P is at least less than 0.05. Arrow (↑) indicates time of injection.

DISCUSSION

The inability of low doses of diphenhydramine (0·7 mg/kg) to affect the CSF levels of 5-HIAA or HVA suggests that sedation and EEG-synchronization are unrelated to an alteration in the balance of 5-HT or dopamine metabolism. It is known that diphenhydramine has anticholinergic properties [14] and anticholinergic drugs have been shown to produce sedation and EEG synchrony [15]. It may be that these effects are associated with the anticholinergic properties of diphenhydramine [1, 16].

Doses of diphenhydramine and phenindamine that produced excitation and tremor elevated levels of 5-HIAA, indicating increased 5-HT metabolism. These data are in harmony with the findings of Grahame-Smith [4], who suggested increased serotonergic activity in a hyperactive syndrome seen after *l*-tryptophan administration in the presence of a monoamine oxidase inhibitor, and Kelly and Naylor [5], who suggested a possible serotonergic role in the production of tremor by harmine. The increased 5-HT metabolism which is temporally related to the production of excitation and tremor (see Figs. 1 and 3) after diphenhydramine and phenindamine suggests a serotonergic interaction in these behaviors. Unfortunately our experimental design does not permit a distinction between an excitatory role for 5-HT under these conditions or excitation of an inhibitory system in response to behavioral activation.

After a convulsant dose of diphenhydramine (30 mg/kg, i.p.), there followed an increase in both 5-HIAA and HVA levels, as well as a fall in rectal temperature. These data agree with the findings of Cooper *et al.* [17] and Schildkraut and Draskoczy [18], who reported an increase in 5-HT and dopamine metabolism after electroconvulsive shock, and of McMillen and Isaac [19], who reported increased 5-HT and dopamine metabolism after pentylenetetrazole convulsions. The time course of 5-HIAA elevation after convulsion with diphenhydramine is of longer duration than the elevation after excitant doses (10 and 20 mg/kg). This persistence of increased 5-HT metabolism may be a reflection of decreased rectal temperature. Isaac [20] has reported that there is an increase in CSF 5-HIAA levels in cats after a lowering of body temperature.

Phenindamine, at a dose of 10 mg/kg, i.p., produced excitation and tremor similar to that seen at 10 or 20 mg/kg of diphenhydramine, as well as producing stereotypic behavior. This effect occurs while both 5-HT and dopamine metabolism are increased. Chiueh and Moore [21] have suggested that *d*-amphetamine and methylphenidate, drugs which produce stereotypy, release dopamine from brain, leading to increased metabolism of dopamine. The increased HVA levels found after phenindamine suggest that the stereotypy may be due to an action on dopaminergic systems.

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