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BRIEF COMMUNICATION

6-Hydroxydopamine-Induced Aggression in Cats: Effects of Various Drugs

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BELESLIN, D. B., R. SAMARDŽIĆ AND S. K. KRSTIĆ. *6-Hydroxydopamine-induced aggression in cats: Effects of various drugs*. PHARMACOL BIOCHEM BEHAV 24(6) 1821–1823, 1986.—The effects of intracerebroventricular injections (ICV) in the unanesthetized cat of antimuscarinic drugs, ganglionic blocking agents, alpha and beta adrenergic blocking substances, dopamine and 5-hydroxytryptamine (5-HT) antagonists, and an antihistamine on aggressive behavior produced by 6-hydroxydopamine injected similarly was investigated. It was found that atropine, hyoscine, hexamethonium, mecamylamine, yohimbine, phenoxybenzamine, propranolol, practolol, chlorpromazine, haloperidol, antazoline and methysergide exerted virtually no effect on the pattern of aggressive responses evoked by ICV 6-hydroxydopamine. It is thus concluded that the aggressive behavior induced by 6-hydroxydopamine is not related to the release of acetylcholine, norepinephrine, dopamine, histamine or 5-hydroxytryptamine from endogenous storage sites in the brain.

6-OHDA Aggression Antimuscarinic drug Ganglionic blocking agents
Alpha and beta adrenergic blocking drugs Dopamine antagoists Antihistamine
5-Hydroxytryptamine antagonist

PREVIOUS biochemical and histological investigations have shown that 6-hydroxydopamine (6-OHDA) injected into the cerebral ventricles (ICV) or cisterna magna depletes the brain of its catecholamines and produces destruction of central catecholaminergic terminals [6, 11, 13, 20]. Further experiments have revealed that 6-OHDA given ICV releases catecholamines from endogenous storage sites [13,14]. 6-OHDA has also been found to have a strong nonspecific releasing action at non-catecholaminergic sites in the brain [14]. In addition to producing biochemical and histological changes, 6-OHDA is known to induce aggressive behavioral effects [4, 5, 8, 10, 17, 18]. Since catecholaminergic, 5-hydroxytryptaminergic and cholinergic mechanisms have been implicated generally in aggressive behavior [2, 3, 15, 16, 19], an attempt was made to study whether postulated catecholamines or other putative neurotransmitter(s) could be associated with the aggressive behavior elicited by ICV 6-OHDA in the cat.

METHOD

In these experiments 118 cats of both sexes (2–4 kg) were used. The animals were anesthetized using sodium pentobarbital (35–40 mg/kg IP). Using aseptic procedures, a hole was drilled 7 to 8 mm rostral to AP zero and 4 to 5 mm from midline. A Collison cannula [9] was then aseptically screwed into the skull. The lower end of the cannula shaft, made of polyethylene tubing with a side opening 1.0 mm from its closed tip, was positioned with the lumen towards the foramen of Monro. Post-mortem dye studies showed that the injected material passed from the lateral ventricle into the third and fourth ventricle. Postoperatively, penicillin was administered intramuscularly, and an interval of five days elapsed before the cats were used for the experiments.

The substances to be injected into the cerebral ventricles were dissolved in sterile, pyrogen-free 0.9% sodium chloride. A test solution was injected manually from a 1.0 ml syringe in a volume of 0.1–0.2 ml over a period of 15–20 sec and washed in 0.1 ml of saline under the same conditions as the drugs following aseptic precautions. The injected animals were observed continuously for a period of 4 hours, and intermittently for 24 hours, each day for a 5- to 8-day period.

In this study, the aggressive response was monitored and measured in a wire mesh cage measuring 110×130×150 cm. On the test day the cat was habituated to the cage for 1.0 hour before any activity was measured. The behavior of the animal, under direct and continuous observation during the experiments, was characterized by absence or presence of

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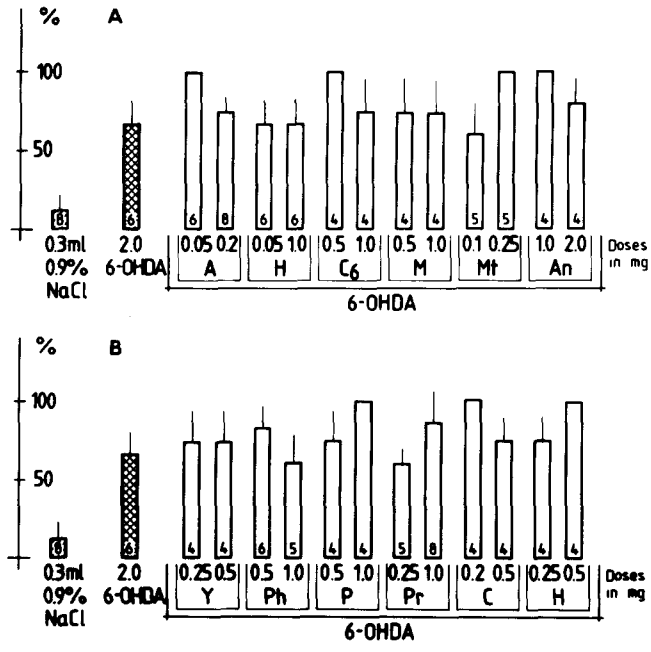

FIG. 1. In A and B effects of atropine (A), hyoscine (H), hexamethonium (C_6), mecamylamine (M), methysergide (Mt), antazoline (An), yohimbine (Y), phenoxybenzamine (Ph), propranolol (P), practolol (Pr), chlorpromazine (C) and haloperidol (H) on aggressive behavior evoked by 6-OHDA. Cross hatched columns represent control experiments. Ordinates: percent of cats showing aggressive behavior. The antagonists were injected ICV in the unanaesthetized cat 20–30 min before ICV 6-OHDA. The number of experiments denoted at base of columns in A and B.

rage, fear, attack, fighting with paws, rearing, threat vocalization, irritability and flight. Measures were taken by two experienced observers, who were blind to the drug condition of the animals, with a correlation coefficient for these checks ranging consistently between 0.94–0.96.

The compounds used were: 6-hydroxydopamine hydrobromide, atropine sulfate, hyoscine bromide, hexamethonium bromide, mecamylamine hydrochloride, methysergide bimaleate, antazoline chlorhydrate, yohimbine chloride, phenoxybenzamine chloride, propranolol chloride, practolol chloride, chlorpromazine chloride and haloperidol. 6-OHDA was always dissolved freshy in 0.9% (w/v) sodium chloride containing 0.2% (w/v) ascorbic acid, whereas haloperidol was dissolved in warm lactic acid. The aqueous solutions of ascorbic acid and lactic acid in a volume of 0.1–0.3 ml had no visible effects on the cat's behavior. All drug doses refer to the salt, except that of haloperidol which refers to the drug.

RESULTS

6-OHDA-Induced Aggression

6-OHDA was injected ICV in doses of 0.5, 1.0 and 2.0 mg every morning for 3 days of 4–6 group-housed cats kept in the same cage.

In 70% of the group-housed cats, ICV 6-OHDA in a dose of 2.0 mg, induced after a period of 1 to 3 days aggressive behavior (irritability, rage, fear, threat, attack, fighting with paws, flight) associated with autonomic (mydriasis, dyspnoea, salivation, piloerection) and motor (ataxia, tremor rigidity, weakness with adynamia, some circling) phemonena (Fig. 1, A and B). The most characteristic sign of aggressive behavior was attack and fighting with paws. If handled, the animals showed rage and sometimes attacked the experimenter with a raised paw. The bouts of attack and fighting with paws usually lasted a few seconds, achieved a maximum 1.0 hour after the ICV injection of 6-OHDA, and continued for 2.0 hours. The frequency of fighting bouts after the third ICV injection of 6-OHDA was reduced and at the same time, motor changes (tremor, ataxia, rigidity, broad-base walking, weakness with adynamia) and sometimes convulsions appeared.

The lower doses of 0.5 and 1.0 mg 6-OHDA in the group-housed cats evoked tremor, ataxia, rigidity, weakness and sometimes convulsions. Only occasionally were restlessness, irritability and rage observed.

Behavioral Effects of 0.3 ml of 0.9% Sodium Chloride

When 0.3 ml of 0.9% sodium chloride was injected ICV every morning for 3 days in group-housed cats (n=8) signs of aggressive behavior were generally not observed. However, in 1 of 8 cats an attack with a raised paw was noted once or twice an hour after the third ICV injection of 0.3 ml of 0.9% NaCl (Fig. 1, A and B).

Effects of Drugs on 6-OHDA-Induced Aggression

Antagonists, antimuscarinic drugs (atropine [0.05–0.2 mg] and hyoscine [0.05–1.0 mg]), ganglionic blocking agents (hexamethonium [0.5–1.0 mg] and mecamylamine [0.5–1.0 mg]), alpha (yohimbine [0.25–0.5 mg] and phenoxybenzamine [0.5–1.0 mg]) and beta (propranolol [0.5–1.0 mg]) adrenergic blocking agents, (practolol [0.25–1.0 mg]), dopamine antagonists (chlorpromazine [0.2–0.5 mg] and haloperidol [0.25–0.5 mg]), a 5-HT antagonist (methysergide [0.1–0.25 mg]) or an antihistamine (antazoline [1.0–2.0 mg]) were injected into the cerebral ventricles 20–30 minutes before the third ICV injection of 6-OHDA. As shown in Fig. 1 A and B, none of these drugs had a significant effect on the fighting with paws evoked by ICV 6-OHDA (2.0 mg) in group-housed (4–8 animals) cats.

DISCUSSION

The results obtained in the present experiments confirmed our earlier reported results that 6-OHDA injected into the cerebral ventricles produces aggressive behavior in the unanesthetized cat [4,5]. Similarly, injections of 6-OHDA into the brain ventricles or into the cisterna magna in the rat and in the mouse induce aggressive behavioral changes such as increased irritability or facilitated aggression [8, 17, 18]. On the other hand ICV 6-OHDA depresses the isolation induced fighting behavior in male mice [7], but an intrahypothalamic injection of 6-OHDA reduces predatory aggression in the rat [12].

The facilitated aggression and increased irritability were correlated with 6-OHDA's effect of depleting brain dopamine and norepinephrine [8,17]. Further, 6-OHDA releases norepinephrine from the endogenous storage sites in the brain [13,14]. Since the adrenergic blocking agents and dopamine antagonists did not prevent the aggressive behavior elicited by 6-OHDA, it is difficult to correlate the release of norepinephrine or dopamine with aggression produced by 6-OHDA. However, 6-OHDA in large doses is known to

release not only norepinephrine and dopamine, but also 5-HT [20] and to have a strong non-specific releasing action on neurotransmitters in the brain [14].

The finding that antimuscarinic drugs, ganglionic blocking agents, a 5-HT antagonist and an antihistamine also did not antagonize 6-OHDA aggressive behavior suggests that the release of acetylcholine, 5-HT and histamine do not account for the mechanism of action of this drug in producing aggressive behavior. Similarly, acetylcholine antagonists, adrenergic blocking agents, a dopamine antagonist, a 5-HT antagonist and an antihistamine fail to inhibit the emotional behavior evoked by ICV d-tubocurarine in the cat [1]. Of course, the possibility exists that 6-OHDA in large doses not only damages catecholaminergic, 5-hydroxytryptaminergic, cholinergic and histaminergic neurones but also other central neurones which release other neurotransmitters responsible for the aggressive behavior. Alternatively, if an imbalance in neurotransmitters produced by ICV 6-OHDA mediates the aggressive behavior, then the balance would be shifted because of the loss of catecholaminergic and serotonergic elements comprising the limbic-forebrain emotional system [16].

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