Pharmacology Biochemistry & Behavior, Vol 24, pp 581–586, 1986 © Ankho International Inc Printed in the U S A 0091-3057/86 $3 00 + 00

Comparative Behavioral Effects of Anticholinergic Agents in Cats: Psychomotor Stimulation and Aggression

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Received 3 July 1985

BELESLIN, D B , K STEFANOVIĆ-DENIC AND R SAMARDŽIĆ *Comparative behavioral effects of anticholinergic agents in cats Psychomotor stimulation and aggression* PHARMACOL BIOCHEM BEHAV **24**(3) 581–586, 1986 —The effect on behavior of eight anticholinergic agents atropine, scopolamine, trihexyphenidyl, biperiden, homatropine, eucatropine, hexocyclium and propantheline, injected into the cerebral ventricle (ICV) of the cat was investigated and compared The anticholinergic agents evoked (1) psychomotor stimulation such as miaowing, loud calling, restlessness, impelling locomotion, jumping, vacant staring, apprehension and loss of interest of the surroundings, (2) aggression, hissing, threat, attack, defense, fighting with paws and flight, (3) autonomic responses including mydriasis, tachypnea, dyspnea, licking, vomiting, salivation, micturition and defecation, and (4) motor phenomena comprising scratching, ataxia, rigidity, tremor, weakness with adynamia or myoclonic jerks Convulsions appeared only after ICV injections of atropine and homatropine The most characteristic behavioral effect of anticholinergic agents was psychomotor stimulation accompanied by mild aggressive responses The only exception was propantheline which caused a muscular weakness and adynamia Atropine and scopolamine alone induced a dose-dependent impelling locomotion as well as fighting behavior Carbachol and eserine injected intracerebroventricularly reversed the locomotion autonomic and motor phenomena produced by anticholinergic agents administered similarly It is suggested that anticholinergic agents acting as partial agonists, can produce their behavioral effects through central cholinoceptive sites

Anticholinergic agents Intracerebroventricular injection Cat Psychomotor stimulation Aggression Central cholinoceptive sites Atropine Scopolamine

PREVIOUS experimental studies have demonstrated that atropine, scopolamine and synthetic antimuscarinic agents applied parenterally or directly into the central nervous system produce profound behavioral changes [1, 2, 3, 16, 19, 23, 27, 33, 35, 36, 37, 38, 39, 42, 43, 44, 47, 48, 49] There are only a few reports however, on the effects of antimuscarinic agents on behavior in cats For instance, it has been shown that atropine and methantheline injected intracerebroventricularly in the cat evoke restlessness, loud calling and unresponsiveness to their surroundings [27] and that scopolamine and N-methyl 4-piperidylcyclobutylphenyl glycolate affect the behavior of cats controlled by an auditory stimulus [37] It was, therefore, of further interest to undertake a quantitative and qualitative evaluation of the behavioral effects of anticholinergic drugs injected into the cerebral ventricles of unanesthetized cats

METHOD

In these experiments, 167 male and femal cats, weighing between 2–4 kg, were anesthetized using sodium pentobarbital (35–40 mg/kg IP) Following aseptic precautions, a hole was drilled 7–8 mm rostral to the zero-line and 4–5 mm from the mid-line A Collison cannula was then screwed into the calvarium, the tip of the cannula resting in the left lateral ventricle [26] The lower end of the cannula shaft was made of polyethylene tubing with a side opening 1 0 mm from its closed tip, and positioned with the lumen facing the foramen of Monro Post mortem dye studies indicated that the injected material passed from the lateral ventricle into the third and fourth ventricle Postoperatively, penicillin was administered intramuscularly An interval of five days was allowed to elapse before an experiment began

Behavioral measures of vocalization, locomotor activity and aggressive behavior were recorded On the tested day, before any behavioral measure was taken, the cat was acclimated to the test environment in a wire-mesh cage measuring 110×130×150 cm, for at least 1 0 hour before intracerebroventricular (ICV) drug injection The behavior of the animals was under direct observation continuously throughout the experiments for a period of 4 hr and intermittently for 24 hours Locomotor activity was measured by counting the number of times the cat crossed from one side of the cage to the other Vocalization, locomotion and fighting responses were scored by two experienced observers who were blind to the drug condition of the animals The correlation coefficient for these checks ranged consistently between 0 82–0 94

Dose-response curves were constructed using linear regression according to the method of least squares Coefficient of correlation (r) of linear regressions was used to determine the existence of dose-responses to drugs

The substances injected ICV were dissolved in sterile, pyrogen-free 0 9% sodium chloride These solutions were

TABLE 1

GROSS BEHAVIORAL EFFECTS FOLLOWING INTRACEREBROVENTRICULAR INJECTIONS OF ANTICHOLINERGIC AGENTS IN UNANESTHETIZED CATS

	Anticholinergic agents								
Effects	atropine 0 2–2 mg	scopolamine 0 2–2 mg	trihexyphedyl 0 2–2 mg	biperiden 0 2–2 mg	eucatropine 0 2–2 mg	homatropine 0 2–2 mg	hexocyclium 0 2–2 mg	propantheline 0 2–2 mg	0 3 ml of 0 9% NaCl
Emotional									
restlessness	+	+	+	+	−	±	±		
miaowing	+	+	±	±	±	±	±	±	±
loud calling	+	+	-	−	±	±	−	-	-
impelling locomotion	+	+	+	±	−	+	±	−	
vacant staring	+	+	−	−	−	±	−	-	−
apprehension	+	+	±	−	−	±	±	−	−
loss of interest of the surroundings	+	+	±	−	±	±	±	±	-
rage	+	+	±	±	±	±	±	±	-
threat	+	+	±	±	±	±	±	±	−
attack	+	+	±	±	±	±	±	±	
defense	+	+	±	±	±	±	±	±	-
fighting with paws	+	+	±	±	±	±	±	±	−
flight	+	+	±	±	±	±	±	±	−
Autonomic									
mydriasis	+	+	+	+	+	+	+	+	−
tachypnea	+	+	+	+	+	+	+	+	−
dyspnea	−	−	−	−	±	−	±	−	−
licking	±	±	±	±	±	±	±	±	−
vomiting	±	±	±	±	±	±	±	±	−
salivation	±	±	−	−	±	±	-	-	-
defecation	±	±	−	−	±	±	±	±	−
micturition	±	±	±	−	±	±	±	±	−
Motor									
scratching	±	±	−	−	−	±	±	−	−
rigidity	-	−	−	−	−	−	-	-	−
ataxia	+	+	+	+	+	+	+	+	-
weakness with adynamia	−	−	−	−	−	−	-	+	-
myoclonic jerks	±	−	-	−	−	±	−		−
convulsions	±	−	−	−	−	±	−	−	−

+=symptom present, ±=symptom inconsistent −=symptom absent
In each injected group n=4–6

then injected by hand 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 with 0 1 ml of saline using aseptic precautions Each cat was used only once in the experiments The compounds used were atropine sulfate, scopolamine bromide, trihexyphenidyl hydrochloride, biperiden hydrochloride, homatropine methylbromide, eucatropine hydrochloride, hexocyclium methylsulfate, propantheline bromide, carbachol chloride and eserine sulfate All drug doses refer to the salts

RESULTS

Behavioral Changes Produced by Anticholinergic Agents

An ICV injection of 0 2–2 0 mg of atropine, scopolamine, trihexyphenidyl, biperiden, homatropine, eucatropine, hexocyclium or propantheline in the unanesthetized cats evoked psychomotor stimulation, miaowing, loud calling, restlessness, impelling locomotion, jumping, vacant staring, apprehension, loss of interest of the surroundings, accompanied with aggression, hissing, threat, attack, defense, fighting with paws, flight, autonomic changes, mydriasis, tachypnea, dyspnea, licking, vomiting, salivation, micturition, defecation, and motor responses, scratching, rigidity, ataxia, tremor, weakness, with adynamia, and myoclonic jerks The main and the most impressive behavioral effect of an ICV injection of an anticholinergic agent was psychomotor stimulation accompanied by mild aggressive changes Convulsions appeared only after atropine and homatropine (see Table 1) The only exception was propantheline, which induced muscular weakness instead of psychomotor stimulation Motor impairment and lack of coordination were so intense that the cats laid on their abdomen or side, however, the muscles were neither flaccid nor spastic

Psychomotor stimulation A few minutes after the intracerebroventricular injection of an anticholinergic agent miaowing occurred, which later became loud calling During loud calling, vacant staring appeared The most pronounced loud calling and vacant staring was evoked by atropine, scopolamine, homatropine and eucatropine Loud calling was characteristic in that it had no visible connection with events in the environment

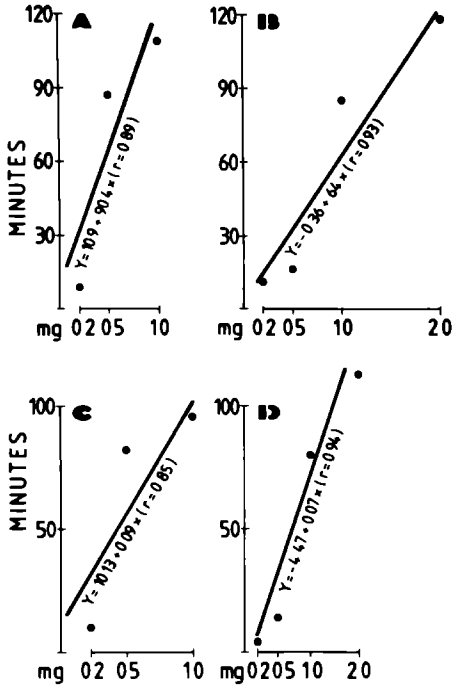

FIG 1 Dose-response relation of atropine and scopolamine injected into the cerebral ventricles of unanesthetized cats on locomotion and fighting A and B locomotion caused by atropine and scopolamine respectively C and D fighting produced by atropine and scopolamine respectively Ordinates duration of locomotion and fighting in minutes Abscissae doses of atropine and scopolamine in mg Each cat was used only once in these experiments Each point is the mean of 4 experiments

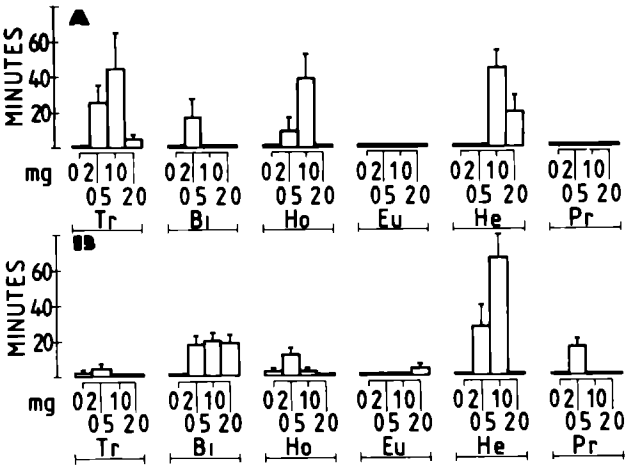

FIG 2 Locomotion (A) and fighting (B) caused by trihexyphenidyl (Tr), biperiden (Bi), homatropine (Ho), eucatropine (Eu), hexocyclium (He) and propantheline (Pr) injected into the cerebral ventricles of unanesthetized cats Ordinates duration of locomotion and fighting in minutes Abscissae doses in mg Each cat was used only once in these experiments Each column represents the mean±SEM of 4–9 experiments

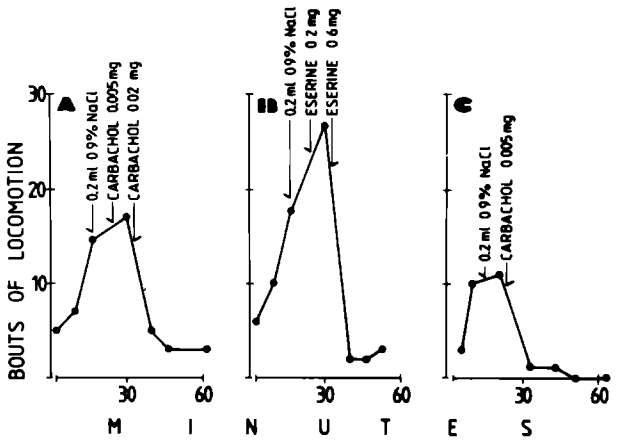

FIG 3 Representative experiments of the effects of carbachol on locomotion evoked by atropine (A), eserine on locomotion caused by scopolamine (B) and carbachol on locomotion produced by trihexyphenidyl (C) in three unanesthetized cats Atropine (0 5 mg), scopolamine (0 5 mg) and trihexyphenidyl (0 5 mg) as well as carbachol (0 005–0 02 mg) and eserine (0 2–0 6 mg) were injected into the cerebral ventricles Consecutive 5 min activity counts were made at 10 min intervals Ordinates bouts of locomotion during each 5 min of a 10 min test Abscissae duration of locomotion in min

The cats, thereafter, wandered around slowly and aimlessly without interest in their surroundings After 10–20 min, the cats became more active and were markedly restless, attempting to escape from the cage They moved without purpose and the excitation was so intense that the cat often jumped in the air or against the side of the cage Only infrequently after ICV injections of atropine and scopolamine did the cat walk against the side of the cage trying to push through it The duration of impelling locomotion was dose-dependent, but only after ICV atropine (r=0 89) and scopolamine (r=0 93) (Fig 1 A and B) Other anticholinergic agents produced a much shorter period of locomotion (Fig 2 A)

Aggression Usually during the second hour after ICV injections of anticholinergic agents, aggressive behavior develops First, the cats were restless, alert, walking or running but ignoring other cats in the cage Thereafter, hissing developed, which was sometimes the only manifestation of aggressive behavior, and usually preceded or was associated with fighting Later, the most restless cat usually sniffed at another cat or cats, attacking with its paws in a single or a series of swift and accurate blows to the neck and the head The attacked cat responded in the same way to the attacker Further, the cats did not show any tendency to maintain the initiated attack and avoided the fighting, whenever possible, so that injuries never occurred The duration of fighting was dose-dependent only after ICV atropine (r=0 85) and scopolamine (r=0 94), although it was of mild intensity (Fig 1 C and D) On the other hand, the fighting produced by intracerebroventricular trihexyphenidyl, biperiden, homatropine, eucatropine, hexocyclium or propantheline was not dose-dependent and was of much shorter duration (Fig 2 B)

Autonomic effects After ICV injections of anticholinergic agents, the autonomic effects, mydriasis, tachypnea, dyspnea, licking, vomiting, salivation, micturition and defecation were observed (see Table 1) These changes preceded or were associated with psychomotor stimulation and aggressive behavior

Motor phenomena Motor phenomena of anticholinergic agents injected into the cerebral ventricles of unanesthetized cats consisted of scratching, ataxia, tremor, rigidity weakness with adynamia and myoclonic jerks (see Table 1)

Convulsions Clonic-tonic convulsions of short duration occurred only when atropine and homatropine were injected into the cerebral ventricles in doses of 2 0 mg (see Table 1)

Carbachol and Eserine and Behavioral Effects of Atropine, Scopolamine and Trihexyphenidyl

The maximal motor hyperactivity usually developed about 60 min after atropine, scopolamine and trihexyphenidyl were injected ICV In this situation, ICV carbachol or eserine reversed the motor hyperactivity evoked by these anticholinergic agents Three typical experiments are shown in FIG 3 A, B and C Apart from locomotor hyperactivity, carbachol and eserine reversed the other symptoms of psychomotor stimulation as well as aggressive behavior, autonomic and motor phenomena

Control Experiments

In all control experiments, injections of 0 3 ml of 0 9% NaCl into the cerebral ventricles did not produce any visible behavioral, autonomic or motor changes

DISCUSSION

As shown in this investigation, anticholinergic agents injected into the cerebral ventricles of unanesthetized cats produced emotional and behavioral changes accompanied by autonomic and motor phenomena Several manifestations of emotional behavior, i e , vocalization, loss of interest of the surroundings, collision with objects, apprehension and flight, associated with autonomic responses and motor phenomena have been described after ICV atropine in cats and dogs [3, 23, 26] In addition, aggressive behavior has been seen in monkeys after parenteral administration of atropine [49]

The results of the present experiments further show that the behavioral effects of eight anticholinergic agents injected ICV in unanesthetized cats are essentially similar The only exception was propantheline which evoked muscular weakness and adynamia instead of psychomotor stimulation Feldberg and Sherwood [27] reported that ICV methanthylene, an anticholinergic agent, also produces lack of coordination and profound motor impairment The most potent psychomotor stimulation and aggressive behavior was obtained after atropine and scopolamine Trihexyphenidyl, biperiden, homatropine, eucatropine and hexocyclium produced also psychomotor stimulation and aggressive behavior which was short-lasting and of mild intensity The duration of psychomotor stimulation and fighting were dose-dependent only after atropine and scopolamine On the other hand, atropine and scopolamine administered subcutaneously in dogs induce behavioral effects which are not dose-dependent The explanation of this observation was that the saturation of both peripheral and central receptors occurred with comparatively low doses of these alkaloids [49] However, in the rat, the motor hyperactivity usually intensifies with increased doses of parenterally administered atropine [44]

In cats, the psychomotor stimulation evoked by ICV or intracerebral injections of morphine, beta-endorphin and d-tubocurarine is not accompanied by aggressive behavioral phenomena [5, 6 11, 12, 14, 17, 21, 25, 34, 40] In this connection, it should be mentioned that the locomotor hyperactivity caused by parenteral administration of atropine and scopolamine in rats is not associated with aggressive behavior [39,44] Moreover, in dogs, parenteral or ICV administration of atropine produces behavioral changes described as a "central anticholinergic syndrome" which consists of vocalization, ataxia, locomotor hyperactivity, loss of interest in surroundings and collision with objects [3, 23, 49]

The aggressive behavior produced by ICV anticholinergic drugs fulfills the basic requirements to be classified as a "fear-induced" aggression [41] A similar type of aggressive behavior is caused by muscarine and 6-OHDA injected ICV in cats, although the aggressive behavior evoked by these agents is more potent and lasts longer [8, 9, 10 13, 15] Atropine and scopolamine administered parenterally in the monkey also produce aggressive behavior [49] On the other hand, atropine and scopolamine depress or abolish the aggressive behavior in the cat evoked by cholinomimetics and anticholinesterases [4,7] as well as the isolation-induced aggression in mice and rats [32,47]

The mechanisms of psychotomimetic effects of anticholinergic agents are not yet clear The findings that anticholinsterases may reverse the behavioral effects of atropine, scopolamine and other anticholinergic agents suggest that these drugs act through central cholinoceptors [22, 29, 31, 33, 36, 45] However, there is evidence that anticholinergic agents affect central dopaminergic mechanisms For instance, it is reported that certain anticholinergic agents, but not atropine and scopolamine, may inhibit the uptake of dopamine in central dopaminergic neurons [20,24] On the other hand, in the present experiments the most potent anticholinergic agents were atropine and scopolamine and, therefore, it is uncertain whether atropine and scopolamine injected ICV produced their behavioral effects by blocking the uptake of dopamine The question thus arises as to how anticholinergic agents in high doses evoke behavioral changes? In peripheral tissues there is evidence that atropine and hyosciamine have cholinergic activity [30 46] Finally, Bradley [18] observed that eserine caused excitation of neuronal activity in the cat's brain-stem independently of the response to acetylcholine Thus, one possible explanation is that anticholinergic agents act on central cholinoceptors as partial agonists

ACKNOWLEDGEMENTS

This research was supported by a grant from the Scientific Fund of the SR of Serbia, Belgrade, Yugoslavia We are most grateful for the gifts of trihexyphenidyl hydrochloride from Schering Corporation (Kenilworth, NJ), biperiden hydrochloride from Knoll Pharmaceutical Company (Whippany, NJ) and hexocyclium methylsulfate from Abbott Laboratories (North Chicago, IL)

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