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Comparison of Circling Induced by Unilateral Intrastriatal Microinjections of Haloperidol, Clozapine and CCK-8 in Rats

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WEISS, F AND A ETTENBERG. *Comparison of circling induced by unilateral intrastriatal microinjections of haloperidol, clozapine and CCK-8 in rats* PHARMACOL BIOCHEM BEHAV 24(4) 983–989, 1986 —The existence of the neuropeptide cholecystokinin (CCK) within a subpopulation of central dopamine (DA) neurons has led to speculations that the peptide may serve as an endogenous modulator of DA functions To test this possibility, the present study examined the pharmacological action of CCK-8 by comparing its effects on DA-mediated circling behavior with those of a typical (haloperidol; HAL) and an atypical (clozapine, CLZ) dopamine antagonist neuroleptic drug. Rats received unilateral intrastriatal infusions of either sulfated CCK-8 (1, 2, or 8 μg), HAL (5 μg) or CLZ (5 or 20 μg) 15 minutes after systemic injection of d-amphetamine (1 mg/kg) Animals were then placed into rotational chambers where the number and direction of complete 360° turns was automatically recorded over a 1 hour session HAL produced strong and almost exclusive ipsilateral circling while the responses after CLZ and CCK-8 were reliably more variable in rotational direction More specifically, the results suggest that CLZ is only a weak antagonist of behaviors mediated by striatal DA activation while CCK seems to be devoid of antidopaminergic properties in the striatum

Clozapine Cholecystokinin-octapeptide Haloperidol Striatum Microinjection

IMMUNOHISTOCHEMICAL research has identified the coexistence of dopamine (DA) and a c-terminal fragment of the gastrointestinal peptide cholecystokinin (CCK) within a subpopulation of mesencephalic (A10 and, to a lesser extent, A9) dopaminergic neurons [22, 34, 35]. Although the precise functional significance of this coexistence is at present unknown, demonstrations that CCK-octapeptide (CCK-8) alters DA turnover [29] and increases the firing rate of A10 dopaminergic neurons [63] have led some to suggest that CCK may serve as a neuromodulator of central DA systems. This hypothesis has generated a great deal of interest particularly in view of the fact that central dopamine neurotransmission has been implicated in a wide variety of normal and pathological behavioral functions [2, 3, 6, 18, 19, 26, 27, 60].

Recently, evidence has accumulated suggesting that sulfated CCK-8 has neuroleptic-like effects in animals and antipsychotic activity in humans; both effects are believed to involve central dopamine substrates [5, 7, 26] In several studies, parenteral administration of CCK-8 (or caerulein, a structurally related decapeptide) produced significant, long-lasting antipsychotic effects in chronic schizophrenic patients ([56, 57, 71], but see [36,50]). Possible involvement of CCK in schizophrenic illness is also suggested by a reported reduction in CCK immunoreactivity in the limbic lobes of schizophrenics [25] In animal studies, CCK-8 has been reported to have effects comparable to those of classical antipsychotic (neuroleptic) agents. For example, the peptide has been found to delay acquisition, and facilitate extinction of active and passive avoidance behaviors [9, 10, 24, 70], and to produce a dose-dependent reduction in exploratory behavior [15], drug-stimulated locomotor behavior ([10, 53, 55, 70], but see [17]), and intracranial self-stimulation [23,69]. CCK-8 has also been reported to potentiate several of the behavioral effects of the dopamine antagonist haloperidol [9, 10, 52].

Although these findings strongly suggest that CCK-8 acts to antagonize DA transmission (i.e., to produce neuroleptic-like behavioral effects), some actions of the peptide appear inconsistent with this view. First, while traditional neuroleptic drugs have potent cataleptogenic actions, such sedative/motoric effects are generally not obtained with CCK-8 ([2, 9, 11], but see [73]). Second, the effects of CCK-8 in another behavioral assay of DA function, the hyperlocomotion-stereotypy model, are inconsistent. Administration of low doses of DA agonist drugs, such as apomorphine or amphetamine, produces a marked increase in general locomotor activity while high doses of these drugs result in the appearance of stereotyped head and limb

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movements and/or compulsive licking/gnawing behaviors [40,51]. Both components of this behavioral response to DA activation are effectively and completely antagonized by traditional neuroleptic drugs [18,51]. CCK-8, on the other hand, has yielded a different psychopharmacological profile In the majority of reports, CCK-8, like the neuroleptics, effectively inhibited stimulant-induced hyperlocomotion [39, 52, 55, 62, 70], but appeared to be a weak inhibitor, at best, of head and limb or orofacial stereotypies ([9, 29, 47, 55, 70, 72], but see [73]) For example, in our own work, intracerebroventricular (ICV) sulfated CCK-8 (2 μg) completely antagonized d-amphetamine-induced hyperlocomotion while causing a slight, but statistically significant, potentiation of head and limb stereotypies [21] These results are particularly interesting in view of the data that suggest that the locomotor component of the behavioral response to amphetamine requires activation of mesolimbic DA mechanisms while the emergence of stereotyped behaviors requires stimulation of striatal DA [13, 14, 15, 40, 43, 45] The antagonism of stimulant-induced hyperlocomotion following CCK-8 administration [21, 39, 52, 55, 62, 70] is therefore consistent with the view that CCK may exert DA antagonist, neuroleptic-like effects in the nucleus accumbens However, the failure of CCK-8 to effectively antagonize stimulant-induced stereotyped behaviors [9, 47, 55, 71, 72] conversely suggests a non-antagonist action in the striatum. This type of differential activity in the nucleus accumbens and striatum has already been proposed to explain the pharmacological actions of the so called "atypical neuroleptics" (e g , clozapine, sulpiride, thioridazine) Like CCK-8, the atypical neuroleptics are ineffective cataleptogenics [12,39], and while potent antagonists of stimulant-induced hyperlocomotion [48,49], they are extremely weak inhibitors of stereotyped behaviors [12,49]. In fact, atypical neuroleptics have, like CCK-8, been reported to potentiate amphetamine-induced stereotypy [32, 48, 61]

It would seem, therefore, that while traditional neuroleptic drugs antagonize behaviors mediated by both the nucleus accumbens and striatum, CCK-8 has only weak, if any, antagonist actions in the striatum To test this hypothesis, we compared the circling behavior induced by unilateral intrastriatal microinjection of CCK-8 to the traditional neuroleptic drug, haloperidol (HAL), and to the atypical neuroleptic drug, clozapine (CLZ), in amphetamine pretreated rats

METHOD

Animals

Fifty-six male Sprague-Dawley rats (Charles River Co.) weighing 350–550 g at the time of surgery served as subjects. The animals were housed individually in a temperature controlled (22°C) colony room on a 12 hr light-dark schedule and received ad lib access to food and water

Drugs

d-Amphetamine sulfate was dissolved in 0.09% saline at a concentration of 2 mg/ml (weight of free base). Haloperidol and clozapine were prepared in vehicle solutions of 0.002 M lactic acid and CCK-8 sulfate ester was dissolved in 0 5 N sodium bicarbonate The injection volume for all intracerebrally administered drugs was 1 0 μl injected over 40 sec.

Surgery

The rats were anesthesized with sodium pentobarbital (50 mg/kg) and stereotaxically implanted with a chronic indwelling stainless steel guide cannula (outer diameter 0 7 mm, Plastic Products Co) With the incisor bar of the stereotaxic instrument (David Kopf Instruments) at 3 3 mm above the interaural line, the coordinates were 0 2 mm anterior to bregma, 3 0 mm lateral and 5 0 mm ventral to the skull surface (Paxinos and Watson [58]) There was a recovery period of 7–9 days after surgery before testing began

Intrastriatal Injection

On test days each animal received a subcutaneous injection of d-amphetamine (1 mg/kg) fifteen minutes prior to the intrastriatal microinjection. These were administered through internal cannulae with an outer diameter of 0 4 mm (Plastic Products Co) which were inserted such that their tips extended 1 mm below the guide cannulae Each internal cannula was connected via PE 20 tubing to a 10 μl Hamilton microsyringe which was driven by a syringe pump (Razel Scientific Instruments, Inc). Injection speed for all drugs was 1 μl over 40 seconds but cannulae remained in place for an additional 30 sec to allow for diffusion away from the injection site Each animal was injected with only one dose of either HAL (0 or 5 μg), CLZ (0, 5 or 20 μg) or CCK-8 (0, 1, 2 or 8 μg) Repeated testing was not conducted so as to avoid problems of striatal damage due to multiple microinjections and of changes in drug sensitivity over time

Measurement of Rotational Behavior

Immediately following intrastriatal microinjections the animals were fitted into light-weight Velcro harnesses and placed into rotational chambers consisting of transparent Plexiglas cylinders (diameter 30 cm) Each harness was connected to a counter mechanism via flexible cable which permitted optimal freedom of movement. The number and direction of complete 360° turns was then automatically recorded by digital counters activated by microswitches Data were collected at 5 min intervals over a 1 hour session

Histology

Upon completion of its single test session, each animal was administered an overdose of sodium pentobarbital and perfused with 50 ml physiological saline followed by 50 ml of 10% formalin. Brains were removed and stored in 10% formalin. Cannulae placements within the striatum were subsequently confirmed from 40 μ cresyl violet-stained frozen sections.

Data Analysis

The percentage of turns that were in an ipsilateral direction during the one-hour test session was analyzed by a two-factor (drugs × time) split-plot Analysis of Variance (ANOVA) Percentages were appropriately corrected by an arc-sine variance stabilizing transformation prior to statistical analysis After confirmation of significant differences in the split-plot ANOVA, the data were collapsed across time intervals and total scores were analyzed by a one-way ANOVA with 7 levels of drug treatment. Significant differences between individual means were then determined by Least Significant Difference (LSD) post-hoc tests.

TABLE 1

MEAN TOTAL NUMBER (±SEM) AND DIRECTION OF TURNS FOLLOWING INTRASTRIATAL INFUSIONS OVER A 60 MIN TEST SESSION

	VEH	HAL	CLZ			CCK-8	
		5 μg	5 μg	20 μg	1 μg	2 μg	8 μg
Mean Total* Ipsilateral Turns	78 5 ± 26 6	132 4 ± 29 4	180 0 ± 37 0	158 6 ± 39 9	98 6 ± 41.8	57 1 ± 19 8	71 8 ± 23.5
Mean Total* Contralateral Turns	86 4 ± 26 8	1 1 ± 0 6	34.5 ± 12 5	36 4 ± 13 2	67 9 ± 22 0	19 1 ± 6 7	51 6 ± 17.8

*n=8/drug group

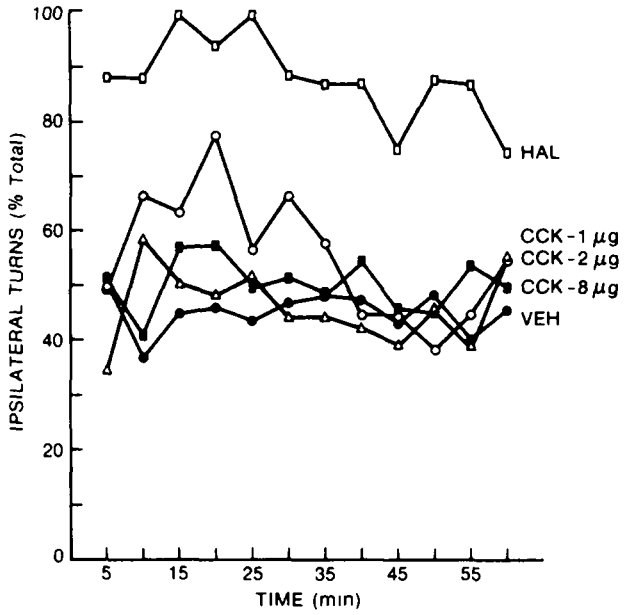

FIG 1 Ipsilateral circling in amphetamine (1 mg/kg, SC) pretreated rats, induced by unilateral infusion of intrastriatal vehicle, haloperidol (5 μg) or CCK-8 (1, 2 or 8 μg) Data are presented as a percent of total number of rotations Each group consisted of eight naive male rats For comparison the HAL and VEH groups are also represented in Fig 2

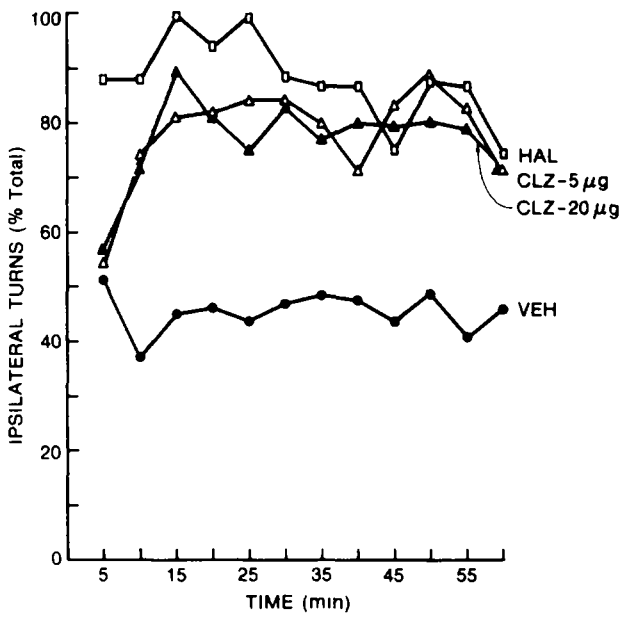

FIG 2 Ipsilateral circling in amphetamine (1 mg/kg, SC) pretreated rats, induced by unilateral infusion of intrastriatal vehicle (VEH), haloperidol (5 μg) or clozapine (5 or 20 μg) Data are presented as a percent of total number of rotations. Each group consisted of eight naive male rats For comparison, the HAL and VEH groups are also represented in Fig 1

RESULTS

Unilateral intrastriatal microinjection of the "traditional" neuroleptic drug, haloperidol, generated strong circling behavior which was almost exclusively ipsilateral to the injection site (mean±standard error number of ipsilateral turns was 132 4±29.4 versus 1 1±0 6 contralateral turns) No other drug condition produced this behavioral profile Table 1 shows the mean absolute number of turns in each direction for each condition and Figs. 1 and 2 illustrate the degree of ipsilateral circling for each group over the course of the 60 min test session All three drug treatments (HAL, CLZ, CCK-8) produced peak behavioral effects between 15 and 20 min post-injection although the magnitude of these effects varied greatly. For example, vehicle-treated animals responded at chance levels (i e., approximately 50% of their turns were in an ipsilateral direction). This was true of both lactic acid and sodium bicarbonate vehicle treatments and the data from these two control conditions were therefore combined CCK-8, at the 2 μg dose, appeared to produce weak ipsilateral turning (Fig. 2) although this effect was not statistically reliable and was no longer present by 40 min post-injection. The two CLZ conditions produced substantial ipsilateral circling that, like HAL, remained throughout the 1-hr test session However, the CLZ groups were still less selective in their direction of circling than the HAL group. The two-factor (group × time) ANOVA computed on the arc-sine transformed data illustrated in Figs. 1 and 2

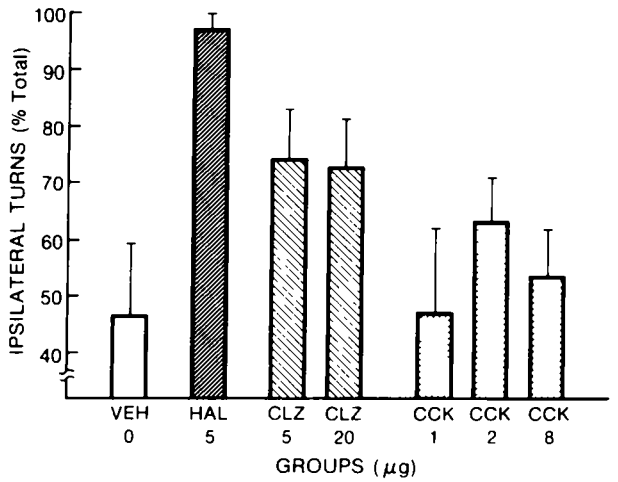

FIG 3 Mean number of ipsilateral turns in amphetamine (1 mg/kg, SC) pretreated rats, produced by each group (n=8/group) during the first 30 min of the test session Data are presented as a percent of total number of turns Least Significant Difference a posteriori tests confirmed that the HAL group was significantly different from each and every other test condition The only other statistically reliable difference was between the CLZ (5 μg) and VEH groups

confirmed significant differences between groups, $F(6,66)=2\ 4$, $p<0.5$

To more easily assess the differences between the various drug conditions, a one-way ANOVA was computed on the mean performance of the subjects during the first half of the test session (i.e., when CCK-8 was still active) These data are presented in Fig. 3 The ANOVA again confirmed that there were highly significant differences between the drug conditions, $F(6,49)=4.8$; $p<0.001$ Post-hoc Least Significant Difference (LSD) tests revealed that only the HAL and the 5 μg CLZ treatments were significantly different from the vehicle condition ($p<0\ 05$), the high dose of CLZ (20 μg) yielded effects that were only marginally significant ($0.1>p>0\ 5$). Significant differences were also obtained between HAL and both CLZ conditions ($p<0.5$)

Although the three drugs proved to have different potencies to elicit ipsilateral circling, there were no significant Drug × Time interactions Figures 1 and 2 show that the time courses of the drug effects were essentially parallel However, in contrast to CLZ and CCK-8 (2 and 8 μg), HAL appeared to have a more rapid onset of action with peak effects between 5 and 15 min post-injection

In summary, while CLZ appeared to produce more ipsilateral turning than CCK-8 (Fig. 1 vs. 2) neither treatment (at any dose) produced a mean performance (during peak effects, i.e., first 30 min) that was comparable to HAL (Fig 3) Although the preference for ipsilateral turns was significantly stronger after CLZ (5 μg) than after vehicle treatment, only haloperidol infusions resulted in a highly selective (mean=97.7% over 1st 30 min) ipsilateral circling behavior that was reliably different from all other conditions.

DISCUSSION

It is well established that circling behavior can be induced by unilateral microinjection of DA agonists or antagonists into the terminal regions of the nigrostriatal pathway [14,68] Such treatments create an imbalance in dopaminergically mediated motor activity between the injected and the uninjected sides Consequently, when further stimulated by amphetamine, the exaggerated asymmetry causes animals to turn (circle) away from the side of greater dopaminergic activity ([41], see also [30, 54, 67]) The vigorous and virtually exclusive ipsilateral circling elicited by haloperidol in the present study presumably reflects effective blockade of dopamine neurotransmission on the injected side and confirms similar data obtained by others [14,68] CCK-8 and clozapine generated response patterns that were clearly different from haloperidol-induced rotation CCK-8, at any dose level, was ineffective in causing significant deviations from vehicle controls Based on these results, we conclude that the peptide may not be a potent antagonist of amphetamine-stimulated striatal DA transmission Ipsilateral circling responses to clozapine at the low (5 μg), but not the high (20 μg) dose, were significantly different from vehicle-treated animals However, compared to HAL, the percentage of ipsilateral turns induced by CLZ was statistically lower than those produced by the HAL-treated rats Although the drug generated a marked preference for ipsilateral circling, it did not suppress contralateral rotation to the extent observed in the HAL condition (i e , HAL animals made 97 7% of their turns in the ipsilateral direction compared to only 74 0% in the CLZ (5 μg) group) In fact, even a 4-fold increase in dose (from 5 μg to 20 μg, see Fig 3) neither decreased the absolute number of contralateral turns nor increased the number of ipsilateral turns With regard to the latter observation it should be noted that peripheral administration of atypical neuroleptics usually requires extremely high doses (compared to typical neuroleptics) in order to produce behavioral effects related to striatal DA blockade [11, 18, 37, 44, 59] In the case of sulpiride, for instance, it has been shown that such high dose regimens may be required because of its poor ability to penetrate the blood brain barrier, but that this compound is equipotent to HAL when injected centrally [37] The present results, however, indicate that centrally applied CLZ is neither equipotent with HAL (at 5 μg) nor able to produce HAL-like behavior at extremely high doses (20 μg) Thus, while CLZ appeared to have antidopaminergic activity in the striatum, its potency was not comparable to that of the traditional neuroleptic drug, haloperidol

It would seem then, that in contrast to HAL, CLZ induced less directionally-specific circling, while CCK-8 was essentially inactive This finding may suggest that CLZ and CCK-8 have relatively weak (or no) DA antagonist actions in striatal brain regions However, both agents have been reported to be potent antagonists of DA-dependent behaviors believed to be mediated by mesolimbic DA substrates (e g , drug-induced hyperlocomotion, conditioned avoidance behaviors and responding for intracranial self-stimulation, [9, 10, 21, 23, 24, 49, 53, 55, 69]) An increasing body of evidence suggests that neuroleptic drugs exert their therapeutic effects via DA receptor blockade in the terminal area of the mesolimbic system (nucleus accumbens) [8, 31, 64, 66] while the extrapyramidal side effects associated with these drugs are due to their antagonism of nigrostriatal DA in the striatum [1, 8, 49, 65] Several investigators have proposed, therefore, that the behavioral actions of atypical neuroleptics may be due to a preferential antidopaminergic activity in the nucleus accumbens (antipsychotic effect, antagonism of drug-induced hyperlocomotion) combined with a weak potency in the striatum (absence of extrapyramidal effects, lack of antagonism of stereotyped behavior and absence of cataleptogenic potency) Although the precise mechanism

for this selectivity is still controversial (e.g., see [14, 26, 42, 48, 66]), the present data are consistent with the notion that atypical neuroleptics may be relatively weak antagonists (compared to traditional neuroleptics) of striatal DA function. This apparent preferential antagonism for mesolimbic DA is even more pronounced in the case of CCK-8. For example, while CCK-8 has little or no antagonist effects on stimulant-induced stereotypy [9, 47, 55, 69, 72], is a weak cataleptogenic agent [2, 9, 10] and does not induce selective ipsilateral circling when injected directly into the caudate (this study)—all related to striatal DA function—it is a potent antagonist of stimulant-induced hyperlocomotion ([21, 39, 52, 55, 62, 70], but see also [17]) and has been reported to be an effective antipsychotic ([56, 57, 71], but see also [36,50])—both actions related to mesolimbic DA function. Such results are, of course, consistent with immunohistochemical data showing that the CCK-DA coexistence is largely confined to mesolimbic neurons [34,35] as well as neurochemical studies in which CCK-8 produced marked changes in mesolimbic, but not striatal DA turnover [46].

The present study was designed to assess the pharmacological actions of CCK-8 on striatal DA function at dose ranges which, in earlier studies, had produced neuroleptic-like effects on behaviors associated with mesolimbic DA [9, 10, 23, 24, 53, 55]. While the majority of behavioral data obtained with CCK-8 at microgram dose ranges suggest that the peptide may have DA antagonist, neuroleptic-like properties, central injection of smaller doses (in the pico- to nanogram range) have been reported to potentiate DA- or apomorphine stimulated behaviors [4,17] and even to mimic the self-administration of amphetamine [33]. The apparent differences between DA antagonist and agonist behavioral actions of CCK-8 cannot, however, be accounted for entirely as a function of the dose since intra-accumbens injection of nanogram doses of CCK-8 have also been shown to attenuate brain stimulation reward [69] and to block apomorphine-stimulated hyperlocomotion [70]—findings which are consistent with DA antagonist activity.

In summary, the present data suggest that the effects of CCK-8 on striatal-mediated behaviors differ from both the typical neuroleptic agent haloperidol and the atypical neuroleptic drug clozapine. Compared to haloperidol, CCK-8 was ineffective while clozapine proved to be less effective (i.e., generated greater variability in rotational direction) in eliciting ipsilateral rotation. These findings, in conjunction with other research, indicate that the putative antidopaminergic properties of the peptide may be limited to mesolimbic dopamine substrates. Moreover, the present results suggest that some of the inconsistencies regarding the neuroleptic-like pharmacological properties of CCK-8 may be related to its inability to directly influence striatal DA transmission

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