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Prevention and Reversal of Dopamine Receptor Supersensitivity by Cyclo(leucyl-glycyl) (CLG): Biphasic Dose–Response Curves

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DRUCKER, G. E., R. F. RITZMANN, L. J. WICHLINSKI, K. ENGH, J. H. GORDON AND J. Z. FIELDS. *Prevention and reversal of dopamine receptor supersensitivity by cyclo(leucyl-glycyl) (CLG): Biphasic dose-response curves.* PHARMACOL BIOCHEM BEHAV 47(1) 141–145, 1994.—Chronic administration (21 days) of haloperidol (HAL) (IP, 1.0 mg/kg/day) induced a behavioral supersensitivity (stereotypic sniffing) to dopamine (DA) agonists (apomorphine) and upregulation (increased B_{max} for sulpiride-inhibitable [^{3}H]spiroperidol binding) of striatal and limbic D_2 DA receptors (DAr). Coadministration of cyclo(leucyl-glycyl) (CLG; 8mg/kg, SC; every third day, every other day, but not every day) with HAL attenuated the behavioral supersensitivity. D_2-DAr binding assays showed 1) that CLG-induced changes in B_{max} parallel these behavioral changes and 2) that the biphasic CLG dose–response curve may involve CLG failure at high cumulative doses to lower B_{max}. CLG also reversed an already established D_2 DAr supersensitivity/upregulation (i.e., when CLG was injected daily for four days after the withdrawal of HAL). CLG alone did not alter behavior or binding. CLG's ability to both prevent and reverse D_2 DAr upregulation/supersensitivity in animal models suggests that CLG may be useful, within a therapeutic window, in clinical disorders that are thought to involve upregulated DAr (e.g., tardive dyskinesia, L-DOPA-induced dyskinesias, and schizophrenia).

D_2 dopamine receptor Supersensitivity Neuroleptics Tardive dyskinesia (TD) Schizophrenia
Cyclo(leucyl-glycyl) (CLG)

PEPTIDE fragments of the C-terminus of oxytocin and their analogs have been shown to have interesting pharmacological properties in animal models. For example, tyr-pro-leu-gly (tyr-MIF) and pro-leu-gly amide (MIF-1) appear to have an antidepressant action (11,12,13,21,27,33). MIF-1, cyclo(leucyl-glycyl) (CLG), and related analogs also prevent the development of tolerance to opioids (e.g., morphine) even though they do not cause analgesia or inhibit binding of opioid ligands in vitro (5,22).

CLG and MIF-1 can also prevent or reverse the development of a dopaminergic supersensitivity, although the mechanism is not known. The dopaminergic hypersensitivities studied include development of a behavioral supersensitivity to dopamine (DA) agonists following 6-hydroxydopamine (28), chronic administration of morphine (29–31), or chronic administration of neuroleptics (1–4,15,16). It also includes induction of an upregulation (increase in receptor density or B_{max}) of D_2 DA receptors (DAr) following chronic morphine (23,24,29,30) or chronic neuroleptics (3,8–10). These chronic in vivo effects of CLG occur without any apparent acute agonist or antagonist action at DAr as measured by locomotion or stereotypy (unpublished), by rotation (1), or by in vitro receptor binding (23).

Although the abilities of CLG and MIF-1 to affect either DA-mediated behaviors or DAr binding have each been studied separately, no one study has systematically correlated the two during prevention or reversal paradigms for a given DA tract. Nor has anyone explored their relation to the known inverted-U-shaped dose–response curve for CLG wherein at the highest doses CLG and related peptides lose their pharmacological effects (6,13,16,19,21). Our study was undertaken in an attempt to fill these gaps in our knowledge by simultaneously monitoring, in a single animal model (chronic neuroleptics), both upregulation of DAr binding and behavioral supersensitivity to DA agonists.

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TABLE 1

EFFECTS OF DIFFERENT CUMULATIVE DOSES OF CLG ON PREVENTION OF HAL-INDUCED BEHAVIORAL SUPERSENSITIVITY TO DA AGONISTS

	Treatment			
CLG	VEH	HAL	HAL/CLG	CLG
E3D	5/120 (4%)	74/120* (62%)	44/120† (37%)	30/120 (25%)
E2D	65/360 (18%)	220/360* (61%)	133/360† (37%)	40/360 (11%)
E1D	46/240 (19%)	150/270* (56%)	92/180* (51%)	29/180 (16%)

HAL was injected daily for 21 days. When given, CLG was injected 30 min prior to HAL either every third day (E3D), every other day (E2D), or every day (E1D). Values are for incidence of stereotypic behavior divided by total number of observations. *$p < .05$ compared to VEH. †$p < .05$ compared to HAL. The n can be calculated by dividing the total number of observations by 10 and was always ≥ 12 rats per group. Overall χ^2 for row 1 = 95.36. Overall χ^2 for row 2 = 249.38. Overall χ^2 for row 3 = 122.36. χ^2 critical = 3.81 for any row. The chi-square test was repeated for comparisons between individual groups.

METHODS

Subjects

Male Sprague-Dawley rats, two months of age at intake, were used. They were housed on a 12 L : 12 D cycle with lights on at 0600. Tap water and standard rat chow were available ad lib.

Drug Administration

Haloperidol (HAL; 1.0 mg/kg, IP) or vehicle (water) was injected daily for 21 days. CLG (8 mg/kg, SC) or vehicle (water) was injected 30 min prior to HAL on several different dose schedules: 1) every third day (E3D), 2) every other day (E2D), or 3) every day (E1D) during chronic administration of HAL. These dose schedules were chosen partly for convenience and partly because, based on the known half-life of CLG of 72 h (20), the cumulative dose of these three groups would differ in the ratio of 1 : 2 : 3. In some experimental groups CLG was injected daily for four days (days 1–4 or 6–9 after withdrawal from chronic HAL).

Behavioral Testing

The incidence of stereotypic sniffing was evaluated 5 or 10 days after withdrawal from HAL (18). Animals were removed from their home cage, injected with apomorphine (APO; 0.5 mg/kg, IP) and placed in a wire mesh cage for observation. All animals were observed for 10 separate 10-s intervals between 10 and 20 min post-APO injection, and the presence of stereotypic sniffing was recorded. Higher order stereotypies such as licking and gnawing, when present, were also scored as a positive result for the presence of sniffing. Stereotypic sniffing was defined as intense, repetitive, purposeless sniffing usually directed towards either the sides or floor of the observation cage. The incidence of stereotypic sniffing was compared statistically between groups using the chi-square statistic. A $p < 0.05$ was considered to indicate significant differences.

Receptor Binding and Analysis

Groups of animals parallel to those in behavioral paradigms were sacrificed on day 5 or day 10 after withdrawal from HAL by decapitation, and the brains were rapidly removed and placed on solid CO_2. Frozen brains were then wrapped in aluminum foil and stored frozen (−80 C) until dissection and assay.

The binding of [^{3}H]spiroperidol ([^{3}H]spiro) to striatal membranes from individual animals or pooled limbic membranes from more than one animal was performed as described previously (17,18). Tissues were homogenized in 100 volumes of 100 mM Na^+/K^+ phosphate buffer, pH 7.4, and centrifuged at $40\,000 \times g$ for 15 min. The resulting pellet was washed twice by resuspending in buffer and centrifugation. Assay conditions were 2 mg (original tissue weight), incubated for 45 min at 37°C, in a final volume of 2.0 ml of phosphate buffer. Nonspecific binding was defined with sulpiride (10^{-5} M). A total of 12 concentrations of [^{3}H]spiro (range 5–500 pM) were used to bracket the predicted K_d value (20 to 80 pM). Ketanserin was not used to mask 5-HT_2-R because binding of [^{3}H]spiroperidol to 5-HT_2-R or to any sites other than the D_2 DAr was considered highly unlikely for several reasons:

1. Sulpiride was used to define specific binding and it is generally accepted that sulpiride has little affinity for 5-HT_2-R or spirodecanone or alpha adrenergic sites.
2. The affinity of [^{3}H]spiroperidol for the 5-HT_2-R is at least 10-fold lower than for the D_2 DAr (26). Moreover, the use of nonlinear analysis contained within our computer program allows the user to factor out any lower affinity sites (25) (see below).

Binding parameters (B_{max}, K_d) were estimated from the [^{3}H]spiro binding isotherms using a nonlinear least-squares regression analysis program (25) based on the independent site models and assumptions of Feldman (14). The statistics of this program are used to select the best model that fits the data (e.g., 1 site vs. 1 site + nonsaturable component vs. 2 sites). Subsequently, ANOVA + post hoc Scheffe's test was used to determine whether group means for B_{max} and K_d parameters were significantly different. A $p < 0.05$ was considered to indicate significant differences.

RESULTS

Chronic administration of the neuroleptic haloperidol (HAL) induced a behavioral supersensitivity to DA agonists

TABLE 2

STRIATAL DAr BINDING DATA FOR RATS TREATED FOR 21 DAYS WITH HAL AND VARIOUS CLG TREATMENT PARADIGMS

Treatment	N	B_{max}	K_d
VEH	16	231 ± 6	57.0 ± 5.2
HAL	16	415 ± 12*	51.4 ± 3.6
HAL/CLG			
E3D	4	280 ± 10†	29.5 ± 9.0
E2D	8	254 ± 9†	33.9 ± 6.3
E1D	6	395 ± 25*	78.1 ± 12.5
CLG			
E2D	10	205 ± 13	29.8 ± 5.3
E1D	6	227 ± 14	53.7 ± 5.4

*$p < .05$ compared to VEH. †$p < .05$ compared to HAL. B_{max} values are in fmol/mg protein for striatal binding of [^{3}H]spiroperidol. K_d is in pM. Statistics: F Test ($F = 34.14$) is indicative of differences in B_{max} values. Post hoc test (Scheffe's) indicates that HAL treatment was significantly different from all other groups. Thus, HAL-induced increase in B_{max} is prevented by concurrent treatment with CLG E3D (every third day), during chronic HAL treatment, and E2D (every other day) during chronic HAL treatment.

TABLE 3

LIMBIC BINDING DATA FOR RATS TREATED FOR 21 DAYS WITH HALOPERIDOL AND CLG AT 8 MG/KG/DAY EVERY OTHER DAY

Treatment	B_{max}	K_d
VEH + VEH	64 ± 6	35 ± 10
HAL + VEH	144 ± 25*	43 ± 14
HAL + CLG	81 ± 9†	48 ± 17
VEH + CLG	93 ± 11	48 ± 25

*$p < .05$ compared to VEH. †$p < .05$ compared to HAL. B_{max} values are in fmol/mg protein for striatal binding of [^{3}H]spiroperidol. K_d is in pM. Chronic haloperidol significantly increased the density of D_2 DAr in the limbic area. This increase was attenuated by the coadministration of CLG (8 mg/kg) every other day during the HAL administration.

(Table 1; also Table 4) and an upregulation of striatal (Table 2) and limbic (Table 3) D_2 DAr. Coadministration of cyclo-(leucyl-glycyl) (CLG) (8 mg/kg, SC) every third day (Table 1, E3D) or every other day (Table 1, E2D) with HAL largely prevented the development of behavioral supersensitivity; this did not occur in the group receiving CLG every day (Table 1, ED). Changes in D_2 dopamine receptor binding in both striatal tissue (Table 2) and limbic tissue (Table 3) were parallel to behavioral changes. Wherever haloperidol-induced behavioral increases had been attenuated by CLG, there was also a decrease in the total number (B_{max}) of D_2 binding sites.

There was no change in affinity ($1/K_d$) for spiroperidol except for a small increase in K_d (decrease in affinity) in subjects that received chronic HAL and then CLG during days 6–9 after withdrawal (Table 4). Chronic CLG by itself changed neither binding nor behavior in any paradigm in this study, nor did it elicit any acute behavioral changes.

When CLG was injected daily (8 mg/kg, SC) on days 6–9 after withdrawal from HAL, CLG was able to substantially reverse the already established behavioral supersensitivity (induced by HAL) to DA agonists (Table 4). This reversal of behavioral supersensitivity was paralleled by a decrease in B_{max} for DAr binding to control levels (Table 4). No reversal of behavioral or binding changes were seen if CLG was administered on days 1–4 after withdrawal from HAL (Table 4). In fact, CLG slightly increased the extent of the behavioral supersensitivity (but not the binding—Table 4).

DISCUSSION

Correlation Between Binding and Behavior

The main findings of this study are that 1) CLG can both prevent chronic haloperidol-induced development of behavioral supersensitivity to DA agonists and reverse an already established supersensitivity and 2) changes in striatal D_2-DAr binding parallel these changes in behavioral supersensitivity (stereotypy) which are mediated by the nigrostriatal DA tract.

TABLE 4

REVERSAL BY CLG OF HAL-INDUCED BEHAVIORAL SUPERSENSITIVITY TO DA AGONISTS

Treatment	Stereotypy	%	B_{max}	K_d
VEH	49/210	23	247 + 29	42 + 10
HAL	187/300*	62	428 + 51*	54 + 6
HAL + CLG (1–4)	65/80†	81	421 + 42*	43 + 5
HAL + CLG (6–9)	40/120†	33	273 + 16	132 + 11*
CLG	49/120	41	240 + 21	49 + 10

For behavioral tests (stereotypy), n can be calculated by dividing the total number of observations by 10 and was always ≥ 8 rats per group. For receptor binding, n values were 6, 9, 6, 6, and 5, respectively. *$p < .05$ compared to VEH. †$p < .05$ compared to HAL. B_{max} values are in fmol/mg protein for striatal binding of [^{3}H]spiroperidol. K_d is in pM. When given, CLG was injected on days 1–4 or days 6–9 after withdrawal from HAL.

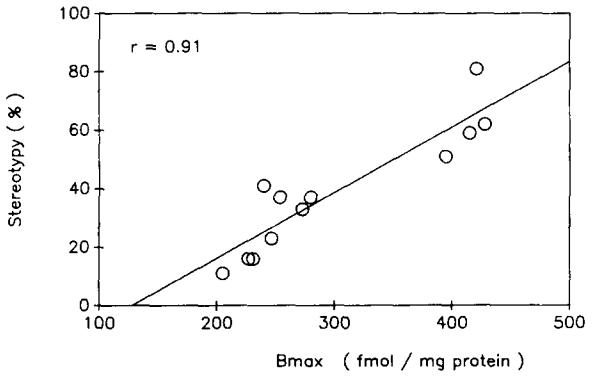

FIG. 1. Correlation between increases in dopamine-mediated behaviors (ordinate) and increases in the number of D_2 dopamine receptors (B_{max}) (abscissa). Behavior was stereotypic sniffing induced by a dopamine agonist (apomorphine, 0.5 mg/kg). The number of dopamine receptors was assayed using [^{3}H]spiroperidol binding in vitro. Each point represents a behavior/binding pair of values from Tables 1, 2, and 4.

Although the prevention and reversal of neuroleptic-induced dopaminergic supersensitivity confirm some previous reports (3,8-10,15,16,23,24), our study demonstrated this effect of CLG, for the first time, in parallel behavioral and binding studies. The positive correlation between downregulation of DAr (CLG-induced decreases in B_{max}) and downregulation of behavior (CLG-induced decreases in APO-induced stereotypy) (Fig. 1, r = .91) strongly suggests that the binding changes cause or contribute to the development of behavioral supersensitivity.

There was no change in affinity ($1/K_d$) for spiroperidol except for a small increase in K_d (decrease in affinity) in subjects that received chronic HAL and then CLG on days 6-9 after withdrawal. In any event, the large decrease in B_{max} in these same animals adequately explains the loss of behavioral supersensitivity.

Biphasic Dose-Response Curves

Several previous studies on behavioral endpoints have indicated that CLG, MIF-1, and related peptides show biphasic dose-response curves (inverted-U shaped) with higher doses becoming less effective (6,16,19,21). We recently reported a similar curve, using mice, for the ability of coadministered CLG to prevent HAL-induced dopaminergic supersensitivity (16). In the present study, using rats, we were able to obtain enough striatal tissue to show parallel biphasic changes in DAr binding.

Lack of changes in striatal D_2-DAr binding are also consistent with the lack of changes in behavior in paradigms where CLG failed to prevent or reverse the supersensitivity. These included a high cumulative dose of CLG, and CLG given on days 1-4 after withdrawal from HAL. It had not been determined previously whether CLG's loss of pharmacological activity at high cumulative doses is due to a failure of CLG to downregulate supersensitive DAr (i.e., to decrease B_{max}) or whether the DAr are still downregulated but some other, as yet unknown, pathways become affected at the higher CLG doses. The data presented here are consistent with the first hypothesis—namely, that at higher doses CLG fails to downregulate DAr.

Reversal of an Already Established Supersensitivity

CLG reversed the HAL-induced supersensitivity when CLG was given on days 6-9 after withdrawal from HAL. Both behavioral and binding parameters were downregulated. When CLG was given during days 1-4 after withdrawal, instead of a reversal there was a slight enhancement of the supersensitivity, although DAr binding did not increase in parallel. One explanation for this failure involves the speculation that CLG might work by increasing DA release (32) into the synaptic cleft. Thus, during days 1-4, when haloperidol is still present and occupying DAr, it would prevent occupancy of the D_2 DAr by the excess DA released by CLG. Another explanation is that CLG reversal is dependent on firing of nigrostriatal neurons and that neuroleptic-induced depolarization block (7,34) of nigrostriatal neurons, which decreases firing, prevents CLG from releasing DA into the cleft and downregulating the supersensitive DAr.

CLG's Mechanism

The mechanism by which CLG affects or fails at higher doses to affect DAr is not known, although it is known that CLG does not appear to have any acute behavioral affects of its own (1) and in vitro does not appear to compete for [^{3}H]spiroperidol binding (24). Obvious possibilities are that CLG works either by postsynaptic and/or by presynaptic mechanisms, although affects on nondopaminergic neurons can not be ruled out at this time.

In this regard, we recently showed that four daily injections of CLG (8 mg/kg, SC) downregulate presynaptic DA autoreceptors (35). Downregulation of autoreceptors is consistent with an increased release of DA into the synaptic cleft, which would be expected to downregulate DAr. However, an allosteric effect by CLG on both pre- and postsynaptic DAr receptor-effector complexes also remains a possiblity.

We have also failed to observe (unpublished) any effect of CLG in vitro (1 nM to 1 mM) on [^{3}H]DA reuptake into synaptosomes, suggesting that CLG probably does not directly inhibit the DA reuptake pump. Additionally, striatal tissue levels of DA (determined by high-pressure liquid chromatography) or its metabolite DOPAC (and the DA/DOPAC ratio) were not significantly changed either 1 or 24 h after a single injection of CLG (8 mg/kg) or 24 h after four daily injections of CLG (8 mg/kg) (unpublished).

Data on the effects of in vivo CLG on in vivo DA release using microdialysis or cyclic voltammetry would obviously be very useful in exploring the mechanism by which CLG downregulates supersensitive DAr.

CONCLUSIONS

Our data indicate that CLG is a novel type of neuromodulator of D_2 DAr and suggest that the ability of CLG to downregulate supersensitive DAr may be useful in disorders that are thought to involve upregulated striatal or limbic DAr, including tardive dyskinesia, L-DOPA-induced dyskinesias, and schizophrenia. The biphasic dose-response curves, however, suggest that there may be a therapeutic window for maximal CLG effects.

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