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Chronic Autoreceptor Blockade and Neuroleptic-Induced Dopamine Receptor Hypersensitivity

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GORDON, J. H., J. K. CLOPTON, J. C. CURTIN AND W. C. KOLLER. *Chronic autoreceptor blockade and neuroleptic-induced dopamine receptor hypersensitivity.* PHARMACOL BIOCHEM BEHAV **26**(2) 223–228, 1987.— Metoclopramide and sulpiride, two benzamide compounds, are equally potent in terms of their ability to block postsynaptic D2 dopamine receptors. However these compounds show a marked divergence in their ability to block dopamine autoreceptors, as metoclopramide is 20–25-fold more potent than sulpiride in blocking these receptors. When injected twice daily for 16 days, metoclopramide at a dose of 10 mg/kg/day will result in the development a postsynaptic dopamine receptor hypersensitivity (i.e., increased behavioral response to apomorphine upon cessation of the chronic treatment). An equivalent dose and treatment schedule with sulpiride has no apparent effect on dopamine receptor sensitivity. Because of the divergent pre- and postsynaptic potency of these two drugs it was possible to construct an autoreceptor "dose response curve" by varying the amount of these two drugs injected. Combinations of these two drugs were chosen so that the level or amount of postsynaptic dopamine receptor blockade was held constant while the amount of dopamine autoreceptor blockade was gradually increased. The results of this autoreceptor blockade "dose response curve" indicated that chronic autoreceptor blockade was involved in the increased dopamine receptor sensitivity that develops upon withdrawal from the neuroleptic drugs. These results suggest that the blockade of dopamine autoreceptors, and perhaps the resulting increase in autoreceptor sensitivity, is an integral component of the neuroleptic-induced dopamine receptor hypersensitivity.

Benzamide Neuroleptic D_2 dopamine receptors Sulpiride Metoclopramide Haloperidol Presynaptic receptors Autoreceptors

SULPIRIDE (SUL), an atypical neuroleptic belonging to the benzamide class, appears to have a decreased potential for inducing dopamine receptor hypersensitivity in animals and for causing tardive dyskinesia in man [8, 21, 35]. Metoclopramide (MET), another benzamide compound, has an effective antipsychotic dose roughly equal to that of SUL and chlorpromazine [32,43]. It is employed clinically for gastric disorders at doses that are about $^1/_{10}$th its effective antipsychotic dose. Even at this lower, non-antipsychotic dose, MET has been reported to induce tardive dyskinesia in man [1, 23, 26, 50]. Thus MET, unlike SUL, may have an increased potential for the adverse side effects that are associated with chronic neuroleptic treatment.

MET and the racemic mixture of (+/−)SUL appear to be equally potent in their ability to displace [3H]-spiroperidol from rat striatal membranes. Although a wide range of IC50 values have been reported, and the (+) and (−) isomers of SUL are different in their potencies [41], when MET and (+/−)SUL are compared in rat striatal membranes by the same laboratory they are equal. The mean IC50 for (+/−)SUL under these conditions (i.e., same laboratory, same tissue, etc.) is 1304 nM and the mean IC50 for MET is 1290 nM [10, 20, 21, 27], while the IC50 for haloperidol (HAL) in these or subsequent reports from the same laboratory is 12 nM [10, 20, 28]. Thus on the basis of their clinical potency [32,43] and competition assays the two benzamides appear to be equal potent and about 100-fold less potent than HAL. At least a portion of the D_2 dopamine receptors are negatively linked to adenylate cyclase, so that the agonist occupation of this population of D_2 dopamine receptors results in the inhibition of adenylate cyclase [27]. This inhibition of adenylate cyclase activity is mediated through a guanine nucleotide binding protein, N_i [24], and the relative *in vitro* potencies of MET and (+/−)SUL in blocking the D_2 dopamine receptors associated with N_i (D_2-N_i) are about equal [31]. The ability of MET and (+/−)SUL to inhibit apomorphine-induced rotation [2] and the hyperactivity induced by intra-striatal injection of dopamine [7] are also simi-

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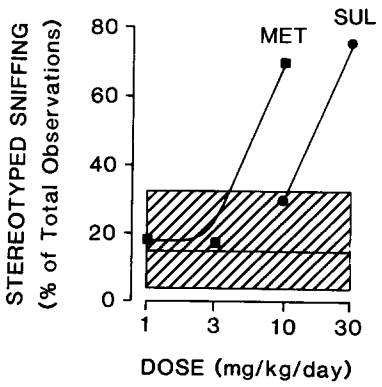

FIG. 1. Dose response curve for sulpiride ((+/−)SUL) and metoclopramide (MET) induced dopamine receptor hypersensitivity. Male Sprague-Dawley rats (6/group) were injected twice daily with (+/−)SUL, MET or vehicle for 16 days. The incidence of stereotyped sniffing, following a 0.25 mg/kg dose of apomorphine, was quantitated on day 22 (i.e., the 6th day of drug withdrawal). The median value and range for the control groups tested during this experimental series are represented by the enclosed striped area. The experimental groups ((+/−)SUL or MET treated animals) which are outside the control range are significantly different from their respective control group (Chi square statistic, p less than 0.05).

lar. These data also suggest an equal potency for these two compounds in terms of postsynaptic dopamine receptor blockade. Therefore the apparent differing ability of these two drugs to induce tardive dyskinesia in man and dopamine receptor hypersensitivity in animals must relate to another aspect of their pharmacology.

Neuroleptics induce tardive dyskinesia and dopamine receptor changes, yet the molecular and/or neural mechanism(s) involved in this receptor modulation are unknown. Dopamine receptors that are blocked by the neuroleptics are found, not only on postsynaptic elements, but also on dendrites, soma and nerve endings of the dopamine neurons. Activation of these presynaptic dopamine autoreceptors will inhibit, the Ca^{++} dependent release of dopamine from the dopamine nerve endings in the striatum [11,33]. The association and/or dependence of these dopamine receptors on Ca^{++} mobilization and/or permeability would suggest that they represent a subpopulation of D_2 dopamine receptors separate for the D_2-N_1 receptors (i.e., the D_2-Ca^{++} dopamine receptor). The possible role that the D_2-Ca^{++} dopamine receptors, and their blockade by the neuroleptics, play in the drug induced dopamine receptor modulation has not been thoroughly investigated. The purpose of this study was to determine the relative potency of (+/−)SUL and MET in blocking the D_2-Ca^{++} dopamine receptors and to evaluate the possible role of this receptor population in the development of the neuroleptic-induced dopamine receptor hypersensitivity.

METHOD

The relative, in vivo, D_2 autoreceptor blocking potency of HAL, MET and (+/−)SUL was determined in male Sprague-Dawley rats, weighing 180–200 grams. Animals were housed 4 to a cage in controlled (12/12) light/dark cycle with free access to food and water. Rats received IP injections of neuroleptic or vehicle, either 30 min ((+/−)SUL and MET) or 60 min (HAL) prior to a 150 μg/kg injection of apomorphine (IP). Immediately following the apomorphine injection the animals were placed in an activity monitor (Columbus Instruments, Opto-Varimax Minor) and the initial, exploratory activity (i.e., beam crossings) were recorded for ten minutes. The ED50 values for the neuroleptics were calculated using the probit transformation methods described by Finney [14].

TABLE 1

ANTAGONISM OF APOMORPHINE-INDUCED HYPOACTIVITY BY NEUROLEPTICS

	Haloperidol	Metoclopramide	Sulpiride
ED50	4.6	20.6	500
95% C. I.	2.1–10.9	10.9–44.5	302–904
Relative Potency	1.0	4.5	109

ED50=Dose of neuroleptic, in μg/kg, required to antagonize 50% of the hypoactivity induced by a 150 μg/kg dose of apomorphine. The ED50 value and the 95% C. I. (confidence interval) for each neuroleptic was estimated from log-probit plots of the dose response curves using the methods described by Finney [14].

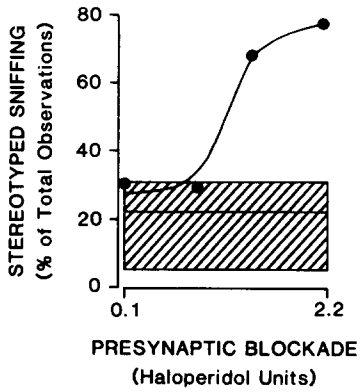

FIG. 2. Relative chronic presynaptic blockade dose response curve. Male Sprague-Dawley rats (6/group) were injected twice daily with one of the dose combinations reported in Table 2 or vehicle for 16 days. The incidence of stereotyped sniffing, following a 0.25 mg/kg dose of apomorphine, was quantitated on day 22 (i.e., the 6th day of drug withdrawal). The median value and range for the control groups tested during this experimental protocol are represented by the enclosed striped area. Haloperidol units are the dose of haloperidol (in mg/kg) which will produce a blockade of presynaptic dopamine receptors equivalent to the blockade resulting from the combination of the two benzamide drugs. The experimental groups which are outside the control range (dose combinations 3 and 4) are significantly different from their respective control group (Chi square statistic, p less than 0.05).

Chronic Treatment Paradigms

Male rats, 180–200 initial weight, were injected with MET, (+/−)SUL, a mixture of these two drugs or vehicle for 16 days, between 8–10 a.m. and 6–8 p.m. Injections were IP at 0.1 ml/100 grams of body weight. Apomorphine-induced stereotypy was evaluated on day 6 of withdrawal from the chronic neuroleptic treatment as previously described ([18], see below).

TABLE 2

DOSES OF METOCLOPRAMIDE AND SULPIRIDE UTILIZED DURING CHRONIC TREATMENT

	Dose (mg/kg/day)		Receptor Blockade (Haloperidol Units)	
	MET	SUL	Presynaptic	Postsynaptic
Dose No. 1	0	10	0.1	0.25
Dose No. 2	1	9	0.3	0.25
Dose No. 3	3	7	0.7	0.25
Dose No. 4	10	0	2.2	0.25

MET=metoclopramide; SUL=(±)sulpiride; Dose No. is the combination of MET and SUL used during the chronic treatments (see Fig. 2). Haloperidol units are the dose of haloperidol, in mg/kg, required to produce an equivalent blockade of either pre- or postsynaptic dopamine receptors. Calculation of the haloperidol units for the presynaptic blockade are based on the relative potency of these three drugs as determined in Table 1. The haloperidol units for the postsynaptic receptor blockade is based on the reported ED50 values for the *in vivo* inhibition of apomorphine-induced circling by these three drugs [2].

Stereotypy

Animals were injected with apomorphine (0.5 mg/kg, IP), and placed in a common holding area. After all the animals had been injected (max of 12 for one observation period), they were placed, randomly, into individual observation cages. This procedure produces a semi-blinded observer as treatment schedules are identified by ear markings after the behavioral tests are completed. Each animal was observed for 10 separate 10 sec intervals during the 10–20 min post-apomorphine period and the presence of specific 'stereotyped' behaviors recorded. Behaviors that were recorded during these observation periods included: locomotor (walking—all four legs moving), grooming, rearing (both front legs off the floor of the cage), climbing (3 or 4 legs grasping the side of the observation cage), head bobbing (head moving up-and-down or side-to-side in repetitive fashion), sniffing (intense 8–10/sec directed towards the sides or floor of the observation cage), licking (licking the wire cage not grooming behavior) and gnawing (chewing the cage wires). The preceding behaviors were scored as present if their duration exceeded 3 sec or continuous if maintained throughout the 10 sec observation period. The total incidence of specific behaviors for experimental groups was compared statistically using the Chi-Square statistic.

RESULTS

The dose response curves for the induction of dopamine receptor hypersensitivity following chronic treatment with either (+/−)SUL or MET are shown in Fig. 1. The minimum chronic daily dose of MET required to induce an increased behavioral response to apomorphine was between 3 and 10 mg/kg per day. The minimum chronic daily dose of (+/−)SUL was between 10 and 30 mg/kg per day. These data indicate at least a three-fold difference in the ability of these two drugs to induce a dopamine receptor hypersensitivity.

The number of beam crossings in control animals (i.e., no apomorphine or neuroleptic) was 1280±160 (mean±S.E.), while the apomorphine treated animals displayed a mean of 320±60 beam crossings in 10 min. All of the neuroleptics tested (i.e., HAL, (+/−)SUL, and MET) readily antagonized this apomorphine-induced hypomotility (Table 1). However the relative potency of these drugs in antagonizing this response was diverse. Haloperidol was the most potent drug tested with an ED50 of 4.6 μg/kg and MET was about 25-fold more potent than (+/−)SUL (Table 1).

Because of the divergence in the relative potency of MET and (+/−)SUL in blocking the D_2-Ca^{++} and the D_2-N_1 dopamine receptors, it was possible to inject combinations of these two drugs where the level of postsynaptic or D_2-N_1 blockade is held constant while increasing the level of presynaptic or D_2-Ca^{++} blockade. The four dose combinations of MET/(+/−)SUL that were used in the chronic administration studies (Fig. 2) are shown in Table 2. The level of postsynaptic dopamine receptor blockade (i.e., D_2-N_1 blockade) was held constant at a dose equivalent to 0.25 mg/kg of HAL. While the level of D_2-Ca^{++} or dopamine autoreceptor blockade was increased from 0.1 to 2.2 mg/kg of HAL equivalents.

The results of this presynaptic or autoreceptor blockade "dose response curve" (Fig. 2) demonstrate the apparent dose dependence of the neuroleptic-induced dopamine receptor hypersensitivity on the level of autoreceptor blockade. These data suggest that increasing the level of chronic autoreceptor blockade is an integral part of the neuroleptic-induced dopamine receptor hypersensitivity.

DISCUSSION

Clinical data indicate that the symptoms of tardive dyskinesia are related to "overactivity" of a central dopaminergic system [44]. This "overactivity" could be related to either an increased synthesis/release of dopamine from the nerve endings, an increased receptor density, or a combination of these two phenomenon. Neuroleptics can increase tyrosine hydroxylase activity and dopamine turnover in the striatum of rats [39, 40, 49], but a tolerance soon develops. Moreover the CSF levels of homovanillic acid (a major metabolite of dopamine) are not elevated in patients with tardive dyskinesia [4], suggesting that an increase in dopamine synthesis or release is not involved in the etiology of TD. However there is an increased sensitivity to the behavioral, biochemical and electrophysiologic effects of dopamine agonists in animals after longterm neuroleptic treatment [5, 13, 16, 17, 30, 44, 49]. This increased sensitivity to dopamine agonists is correlated with an increased number of binding sites in the striatum, for both dopamine agonists and antagonists [5, 13, 19]. Responses mediated by the dopamine autoreceptors or the D_2-Ca^{++} dopamine receptors may also be enhanced by chronic neuroleptic treatment. The chronic administration of haloperidol or fluphenazine has been reported to increase the sensitivity of the dopamine neurons in the substantia nigra to iontophoretic or intravenous administration of dopamine and apomorphine [15,34]. Moreover chronic administration of haloperidol will enhance the inhibitory effects of apomorphine on locomotor activity [45] and on dopamine turnover in nigro-striatal neurons [17, 37, 40]. The *in vitro* inhibition of dopamine release via the activation of the presynaptic dopamine autoreceptors of the nigro-striatal dopamine neurons has been reported to be enhanced in rabbits following chronic HAL [11,33]. Thus available data suggest that the dopamine autoreceptors, like the postsynaptic dopamine receptors, are modulated by chronic neuroleptic treatment.

The data presented in Fig. 1 indicate that MET is three

times more potent than (+/−)SUL for the induction of dopamine receptor hypersensitivity in rats. MET and (+/−)SUL are much less potent than HAL as more than a 100-fold increase in the median daily dose is needed for these drugs to be clinically effective as antipsychotics [32, 41, 43]. The relative potency of these agents in displacing [3H]-spiroperidol from rat striatal membranes parallels their reported antipsychotic potencies [41]. Moreover, similar or equivalent relative potencies have been observed for these two drugs in the antagonism of apomorphine-induced turning behavior [2], intrastriatal dopamine-induced hyperactivity [7] and dopamine mediated inhibition of adenylate cyclase [31]. In general all of these responses are thought to represent the actions of dopamine at postsynaptic dopamine receptors. Thus it would appear that the ability to block postsynaptic dopamine receptors, or more precisely, the ability to block the D_2-N_i receptors is not directly associated with the development of the neuroleptic-induced dopamine receptor hypersensitivity.

Although MET and (+/−)SUL appear to have equal postsynaptic receptor blocking potencies [7, 21, 22, 32, 41], available data suggest that MET is more potent than (+/−)SUL in antagonizing dopamine autoreceptor mediated responses [2, 6, 7]. For example the ability of neuroleptic drugs to block apomorphine-induced decreases in L-dopa accumulation in rats pretreated with dopa decarboxylase inhibitor (NSD-1015) and gamma-butyrolactone has been proposed to represent the interactions of dopamine agonists and antagonists at the level of the presynaptic dopamine autoreceptors [3, 6, 48]. MET is more potent than (+/−)SUL in blocking the apomorphine-induced accumulation of L-dopa in this proposed presynaptic assay [2]. Similarly the ability of apomorphine to inhibit locomotor activity in rats and mice is thought to represent dopamine autoreceptor stimulation [31, 36, 42]. Our data confirm this divergence in the relative autoreceptor blocking potency of these two drugs as MET is roughly 20-fold more potent than (+/−)SUL in blocking the apomorphine-induced hypoactivity (Table 1).

This divergence in relative potency of (+/−)SUL and MET in blocking the dopamine autoreceptors may explain the difference in the ability of these two drugs to inhibit complex behaviors such as apomorphine-induced stereotypy [32]. Apomorphine-induced stereotypy may also involve D_1 dopamine receptors [47] thus the inhibition of some of the components of this complex behavior may represent the blockade D_1 dopamine receptors. Alternatively, D_2-Ca^{++} dopamine receptors (i.e., dopamine receptors linked to the mobilization of Ca^{++} and/or neurotransmitter release) in addition to being located on the dopamine neurons (i.e., the dopamine autoreceptors) may also be located postsynaptically to the dopamine neurons [9] and thus could be involved in various components of complex behaviors (i.e., stereotypy, catalepsy, etc.) where the potency of MET and (+/−)SUL are divergent. For example, the reported enhancement of some components of stereotypy by SUL [38] could be explained on the basis of its relatively greater potency at the D_2-N_i vs. the D_2-Ca^{++} receptors. In other words behaviors that are dependent upon the D_2-N_i could be blocked while the behaviors mediated by the D_2-Ca^{++} could still be expressed.

The greater relative potency of MET in blocking dopamine autoreceptors, *in vivo*, allowed us to construct a dopamine autoreceptor blockade "dose response" curve, where the level of chronic D_2-N_i dopamine receptor blockade is held constant, while increasing the level of dopamine autoreceptor or D_2-Ca^{++} receptor blockade (Table 2). The results of these four drug combinations demonstrate that increasing the level of dopamine autoreceptor blockade resulted in the development of a dopamine receptor hypersensitivity. Because the level of D_2-N_i receptor blockade was held constant it would appear that some level of autoreceptor or D_2-Ca^{++} receptor blockade is required before chronic drug treatments will result in the development of a dopamine receptor hypersensitivity. The exact or relative level of blockade and the role of these two D_2 receptor subpopulations in the neuroleptic-induced dopamine receptor hypersensitivity remain to be determined.

It is intriguing to speculate that the development of a dopamine autoreceptor hypersensitivity is an integral step in the development of a neuroleptic-induced dopamine receptor hypersensitivity. Once the presynaptic dopamine autoreceptors have increased their sensitivity (i.e., become hypersensitive) then less dopamine will be required to activate these inhibitory autoreceptors, resulting in a chronic state of decreased release and/or synthesis of dopamine. It might be noted that clinical data support the hypothesis of a decreased release of dopamine as patients suffering from TD appear to have below normal CSF levels of HVA [4]. This chronic decrease in the release of dopamine, once established, would in turn result in a decrease in the down-regulation of both pre- and postsynaptic dopamine receptors by endogenous dopamine. Thus, once initiated, an increased dopamine autoreceptor sensitivity could become a self sustaining phenomenon resulting in both the development and the maintenance of a chronic receptor hypersensitivity at both pre- and postsynaptic receptor sites. The overall activity of a transmitter system is dependent not only on the postsynaptic receptor density but also on the amount of available or released transmitter. Thus the behavioral symptoms of "excess transmitter activity" would not be apparent until the release of the dopamine has reached some basal level, such that the next increase in postsynaptic receptor density can not be compensated for by decreasing release and/or synthesis of endogenous dopamine. In other words the symptoms of TD appear only when the endogenous neural mechanisms can no longer compensate for the drug effects.

Commonly used animal models of tardive dyskinesia do not display spontaneous abnormal movements, which has been considered a limitation, but which is more consistent with the human syndrome where the motor abnormalities appear only after prolonged treatments. The "classic" dopamine receptor supersensitivity hypothesis as the mechanism of neuroleptic action in the development of TD has been challenged [12,46]. Alternative hypotheses are needed, but the suggestion that the neuroleptics have a selective neurotoxic action [12] is neither parsimonious nor supported by current data. By expanding the actions of the neuroleptics to include the dopamine autoreceptors many of the proposed discrepancies [12] between the animal models and the human syndrome can be explained.

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