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Neurotransmitter System Interactions Revealed by Drug-Induced Changes in Motivated Behavior

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MONTGOMERY, A. M. J. AND A. J. GROTTICK. *Neurotransmitter system interactions revealed by drug-induced changes in motivated behavior.* PHARMACOL BIOCHEM BEHAV **62**(4)643–657, 1999.—The present article reviews studies conducted either in collaboration with Jac Herberg, or in parallel with those studies that used consummatory behavior and responding for intracranial self-stimulation (ICSS) to investigate interactions between neurotransmitter systems. The studies reviewed include investigations of the role of dopamine in 8-OH-DPAT–induced feeding; the role of 5-HT_3 receptors in the stimulant and depressant effects of nicotine on responding for ICSS; the interaction of D_2 and 5-HT_2 antagonists in sucrose consumption, and the differential contributions of α_2-adrenoceptor and 5-HT_2 antagonism to the rapid recovery of ICSS responding from depression produced by atypical neuroleptics. Further studies of the role of α_2-adrenoceptor antagonism in the pattern of response decrements produced by neuroleptics on schedule-controlled responding for food confirm that the behavioral effects of monoamine interactions vary, depending on the specific receptor subtypes targeted and the behavioral paradigm employed. Consequently, the clinical relevance of findings will crucially depend on the choice of appropriate behavioral measures. © 1999 Elsevier Science Inc.

Dopamine–serotonin interactions α_2-Adrenoceptor antagonism Feeding Intracranial self-stimulation Operant responding

A primary aim of psychopharmacology is to investigate the behavioral effects of drugs and how these effects are mediated by changes in neural activity. For the most part, this has meant that psychopharmacologists have preferred to use the most selective drugs available, so they can be confident that any observed behavioral change resulting from drug treatment reflects a change in activity of the transmitter system targeted by the chosen drug. However, any given behavior is likely to be influenced by a number of transmitter systems, for example, feeding behavior is modified by drugs acting on serotonin (5-HT), dopamine (DA), and noradrenaline (NA) systems, among others. Clearly, transmitter systems do not work in isolation, but rather they interact with one another so that one system might excite, inhibit, or modulate another. Consequently, the role of transmitter interactions in the regulation of behavior has become the subject of increasing attention.

For the last 12 years we have been collaborating with Jac Herberg, and much of our work during that time has been designed to investigate monoamine interactions, primarily between DA and 5-HT (and more recently NA), and their influence on motivated behavior. In particular, we have investigated the contribution of 5-HT/DA interactions to the regulation of feeding and responding for intracranial self-stimulation. The foundations of this work lie in a well-documented inhibitory link between serotonergic activity and dopaminergic function [(e.g., 28,86,161,162)]. Potential anatomical substrates for 5-HT/DA interactions include projections from the raphe nuclei to the substantia nigra, ventral tegmental area, nucleus accumbens, and striatum, which provide a basis for biochemical, electrophysiological, and behavioral evidence that inhibition of 5-HT cells in the raphe has a disinhibitory effect on DA activity (24,49,140).

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Over the period of our collaboration understanding of the diversity of 5-HT receptors has increased, so that the original distinction between M and D receptors (65) has been superseded by a scheme consisting of seven receptor types, many of which have a number of subtypes (87). To date our interest has been limited to 5-HT_{1A}, 5-$HT_{2/2C}$, and 5-HT_3 receptor ligands and their effects on DA-mediated changes in feeding and self-stimulation behaviors, although more recently we have turned our attention to the role of α_2-adrenoceptor ligands and their contribution to the behavioral effects of atypical neuroleptics. The present article reviews our work in these areas. Most of this work was carried out in collaboration with Jac Herberg, and the remainder was subject to his influence, although he was not always credited for his contribution.

Behavioral Responses to 8-OH-DPAT

8-OH-DPAT is a selective agonist at the 5-HT_{1A} receptor (70,107,130). Among the earliest behavioral studies using 8-OH-DPAT was one demonstrating an increase in male sexual behavior and another demonstrating an anticonflict effect (3,53). However, interest in 8-OH-DPAT grew enormously when it was reported to have a biphasic effect on spontaneous feeding behavior: low doses enhance food intake, but higher doses inhibit it (44,45). The hypophagic response to higher doses was not surprising, because the supposed role of 5-HT in mediating satiety (10) is well known, but the hyperphagic response to low doses was unexpected. Subsequent studies indicated that at low concentrations 8-OH-DPAT binds selectively to somatic autoreceptors (85) and acts to inhibit 5-HT cell firing in the dorsal raphe (47). A straightforward interpretation of these results suggested that 8-OH-DPAT stimulates appetite in a specific manner by counteracting the tonic serotonergic inhibition of feeding (46). However, from the outset there were clues that 8-OH-DPAT–induced feeding might require a more sophisticated explanation. In the first place, it had previously been reported that low doses of 8-OH-DPAT facilitate male rat sexual behavior (3), indicating that the enhancement of consummatory responses by 8-OH-DPAT was not limited to feeding. Second, in nondeprived rats the latency to eat following injection of low doses of 8-OH-DPAT (15–125 μg/kg) was greatly increased (44). If 8-OH-DPAT acts by stimulating appetite, it is hard to see why it should take so long for the rats to start eating.

Consideration of these points led Jac Herberg to suggest to us that 8-OH-DPAT–induced feeding might be secondary to a form of dopaminergically mediated nonspecific behavioral activation: mild stressors, including tail pinch, result in an increase in arousal and an increase in responsiveness to salient environmental stimuli (4). These effects are mediated by an increase in DA activity, and are associated with increased feeding or wood-block gnawing and facilitation of male rat sexual behavior, but no increase in water intake (4,135,169). A similar increase in feeding has been reported after treatment with low doses of either amphetamine or apomorphine (11,40,52,167), again implicating increased DA activity in the hyperphagic response to nonspecific behavioral activation. For these reasons we decided to look more closely at the behavioral effects of 8-OH-DPAT.

Effects of 8-OH-DPAT on Consumption of Wet Mashes and Liquid Diets, and Gnawing on Wood Blocks

In our first study we sought to determine the behavioral specificity of 8-OH-DPAT. To this end we investigated the effects of 8-OH-DPAT on intake of sweetened and unsweetened wet mashes, in deprived and nondeprived rats. This was followed by tests of its effects on intake of various caloric and noncaloric liquids and on the duration of wood block gnawing (114) (see Table 1)

On test days the feeding session began with a 10-min preexposure to the test diet, which we have found promotes satiety and reduces subsequent consumption (unpublished findings). This procedure reveals more clearly any antisatiety effect of drug treatments. Initial experiments confirmed that in 1-h tests, 60 μg/kg 8-OH-DPAT substantially increased wet mash consumption. Despite large differences in preexposure intakes, this was true for nondeprived and 20-h food-deprived rats, and for nondeprived rats tested with sweetened (5% sucrose substituted for tap water) wet mash. However, this apparently robust effect was not seen when liquid test diets were used: in a second experiment, 8-OH-DPAT (15–60 μg/kg) did not significantly alter the consumption of 0.9% saline, 5% sucrose or 0.1% saccharin. Because it could be argued that none of these liquid diets provide a substantial calorie load, the experiment was repeated using a 35% sucrose solution. Again, there was no significant increase in total intake, and this remained the case even when the dose range was doubled to include a dose of 120 μg/kg and the test period was increased to 3 h. In case there was something unusual about sucrose, further tests were conducted using milk and a high-protein liquid diet (Casilan). Yet, again, 8-OH-DPAT (30–120 μg/kg) failed to increase total intake and, far from being increased, consumption of the high-protein liquid diet was suppressed. Although it is clear that 8-OH-DPAT can increase liquid consumption under certain circumstances (42,43,60,99,119) our results and others (57) raise problems for the proposal that 8-OH-DPAT increases intake by opposing a serotonergic satiety signal. If that were the case, 8-OH-DPAT should enhance

TABLE 1

TEST CONDITIONS AND RESULTS FOR STUDIES OF THE EFFECTS OF 8-OH-DPAT ON FOOD INTAKE, LIQUID INTAKES, AND WOOD BLOCK GNAWING

DPAT Dose (μg/kg)	Diet	Food Dep	Change in Total Intake	Test Interval (min)	BSS
60	wet mash	20h	increased ($p < 0.001$)	60	yes
60	wet mash	none	increased ($p < 0.001$)	60	no
60	sweetened wet mash	none	increased ($p < 0.001$)	60	yes
15–60	0.9% saline	none	none	60	no
15–60	0.1% sacc	none	none	60	no
15–60	5% sucrose	none	none	60	
15–60	35% sucrose	none	none	60	yes
30–120	35% sucrose	none	none	180	no
30–120	milk	none	none	60	no
30–120	liquid protein	none	decreased ($p < 0.001$)	60	no
60	wood blocks	none	increased gnawing ($p < 0.01$)	25	no

All tests incorporated a 10-min period of access to the diet prior to drug treatment. Details of changes to behavioral satiety sequence (BSS) parameters can be found in the text.

intake of all caloric substances regardless of whether they are solid, liquid or powdered, sweet or savory.

In the original demonstration of 8-OH-DPAT–induced feeding, rats were given access to three food pellets and three wood blocks, each of a similar size to the food pellets (44). The idea behind this was to test for nonspecific drug-induced gnawing. The results indicated that, given this choice, the rats spent very little time gnawing the wood blocks. In our study (114) the effects of 8-OH-DPAT treatment on wood block gnawing were tested in the absence of food. Under these circumstances there was a greater than threefold increase in the duration of gnawing (vehicle condition 15 s; 60 μg/kg 8-OH-DPAT 52 s), which was in keeping with the results of a similar study (57). Although this increase in gnawing is probably too modest to explain the 8-OH-DPAT–induced increase in food consumption, a "chewing" account might contribute to an explanation of our failure to find any increases in consumption of liquid diets. In any event, the observation that 8-OH-DPAT increases wood block gnawing does provide further support for the proposal that the behavioral responses to 8-OH-DPAT resemble those resulting from tail pinch.

8-OH-DPAT and the Behavioral Satiety Sequence

Further problems emerged when a more sophisticated analysis of the effects of 8-OH-DPAT on the structure of feeding behavior was conducted (114). As animals feed to satiety, they exhibit a characteristic sequence of behavioral changes: in the rat, the cessation of feeding is followed by a period of exploratory behavior and grooming, which is soon superseded by resting or sleep (5,98). Under our control conditions this "behavioral satiety sequence" was reliably observed in animals consuming wet mash, sweetened wet mash, and 35% sucrose (see Table 1). In 20-h food-deprived rats 8-OH-DPAT prolonged feeding and delayed resting, which would be consistent with an antisatiety effect. However, in nondeprived animals given access to wet mash, feeding in the early part of the session was suppressed, resulting in an increased latency to start eating, and activity was the initial predominant behavior. As with the effects on liquid diet consumption, these effects cannot readily be reconciled with the notion that 8-OH-DPAT inhibits satiety. Moreover, the parallels between behavioral responses to 8-OH-DPAT and tail pinch raise the possibility that 8-OH-DPAT–induced behavioral changes, like those produced by tail pinch, are mediated by an increase in DA activity (4,135,160), particularly because 8-OH-DPAT–induced gnawing has been blocked with haloperidol (57). Consequently, we set out to determine whether 8-OH-DPAT–induced feeding would be blocked by DA antagonists.

Blockade of 8-OH-DPAT–Induced Feeding Behavior by DA Antagonists

Apart from the apparent similarities between the behavioral effects of 8-OH-DPAT treatment and tail pinch there are other reasons for suspecting a mediating role for DA in the behavioral effects of 8-OH-DPAT. A number of authors had reported that eating or chewing can be elicited by drugs that stimulate postsynaptic DA receptors (11,26,40,52,54,94,167), and more persuasively, the DA antagonist spiroperidol, suppressed 8-OH-DPAT–induced feeding (88). At the time, the authors were apparently reluctant to ascribe this finding to the DA antagonist properties of spiroperidol, preferring to ascribe it to an antagonist effect at 5-HT_{1A} receptors.

In some initial experiments (117) we established the effects of a range of doses of 8-OH-DPAT (30–120 μg/kg) on consumption of lab chow pellets in nondeprived rats. The results revealed that the single dose of 30 μg/kg 8-OH-DPAT increased food intake. In subsequent experiments both sulpiride (a D_2 antagonist) and SCH-23390 (a D_1 antagonist) blocked the hyperphagic response to 8-OH-DPAT (30 μg/kg) in nondeprived rats and in 4-h food-deprived rats (see Table 2).

Analysis of the behavioral satiety sequence for the 4-h food-deprived rats confirmed that 8-OH-DPAT prolonged feeding and delayed the onset of resting, results that are compatible with the proposal that 8-OH-DPAT inhibits satiety. The significant increases in feeding times were reversed by both sulpiride and SCH-23390, neither of which in themselves affected feeding time. In nondeprived rats the effects of 8-OH-DPAT were somewhat different. In the control condition, eating was observed infrequently, and activity was the predominant initial behavior; as activity declined over the first 15 min it was superseded by resting. 8-OH-DPAT greatly prolonged the period of activity, and there were two peaks of eating behavior (one in each half of the test period) and a gradual increase in resting throughout the second half of the 1-h test period. Overall, 8-OH-DPAT increased activity and decreased resting, and both of these effects were reversed by both sulpiride and SCH-23390.

These results clearly demonstrated that the effects of 8-OH-DPAT on food intake, and on the behavioral satiety sequence measures, were antagonized by both sulpiride and SCH-23390. At the doses used, sulpiride and SCH-23390 did not in themselves reduce food intake. Although SCH-23390 does have a weak affinity for 5-HT_1 receptors (31,89) at the dose used in this study, sulpiride has not been reported to bind to 5-HT receptors, so these data provide strong support for our proposal that the hyperphagic response to 8-OH-DPAT is mediated by an increase in DA transmission, possibly at the D_1 receptor and certainly at the D_2 receptor. Although SCH-23390 binds specifically to D_1 receptors, it is also known to block certain functional effects of D_2 receptor stimulation (13,134,159), so it is probable that the hyperphagic effect of 8-OH-DPAT depends on D_2 rather than D_1 receptors. Further support for dopaminergic mediation of the behavioral effects of 8-OH-DPAT is provided by the findings that haloperidol blocks 8-OH-DPAT–induced chewing (57), and dopamine antagonists block 8-OH-DPAT–induced feeding, even when the 8-OH-DPAT is injected into the dorsal raphe nucleus (59). Furthermore, neurochemical, electrophysiological, and behavioral evidence that 8-OH-DPAT stimulates central dopamine transmission has been reported (33), and most convincingly, injection of α-flupenthixol into the nucleus accumbens has been shown to attenuate the feeding response to 8-OH-DPAT injected into either the dorsal or median raphe (58).

It is well established that 8-OH-DPAT elicits feeding by an action at inhibitory somatic autoreceptors of 5-HT cells in the dorsal raphe nucleus (46,47). Our experiments on 8-OH-DPAT–induced feeding suggest that, following the inhibition of activity in 5-HT neurons, a secondary disinhibition of DA activity forms an essential step in the expression of feeding behavior. Furthermore, parallels between the behavioral effects of 8-OH-DPAT, low doses of amphetamine, and tail pinch suggest that the hyperphagic effect of 8-OH-DPAT depends on nonspecific behavioral activation rather than an antisatiety effect of reduced serotonergic function.

Effects of 8-OH-DPAT on Self-Stimulation Responding

If the behavioral effects of 8-OH-DPAT depend on a secondary disinhibition of DA activity, then responding for brain

TABLE 2
TEST CONDITIONS AND RESULTS FOR STUDIES OF THE EFFECTS OF 8-OH-DPAT ON FOOD INTAKE

DPAT Dose (μg/kg)	Diet	Food Dep	Change in Intake	Test Interval (min)	BSS	Additional Comments
30–120	wet mash	none	30μg/kg increased ($p < 0.01$)	60	no	decreased by 120 μg/kg
30–120	lab chow	none	30μg/kg increased ($p < 0.01$)	60	no	
30 (+Sulp)	lab chow	none	increased ($p < 0.01$)	60	yes	blocked by sulpiride
30 (+ SCH)	lab chow	none	increased ($p < 0.01$)	60	yes	blocked by SCH-23390
30 (+ Sulp)	lab chow	4 h	increased ($p < 0.05$)	60	yes	blocked by sulpiride
30 (+ SCH)	lab chow	4 h	increased ($p < 0.05$)	60	yes	blocked by SCH-2330

8-OH-DPAT-induced changes to feeding and behavioral satiety sequence (BSS) measures were reversed by pretreatment with either sulpiride (Sulp) or SCH-23390 (SCH). Details of changes to behavioral satiety sequence (BSS) parameters can be found in the text.

stimulation reward should be affected by 8-OH-DPAT: threshold current self-stimulation is particularly sensitive to alterations in dopaminergic transmission (66,136); on the other hand, self-stimulation has usually been found to be much less sensitive, or completely insensitive, to quite severe decrements in 5-HT transmission, whether brought about by lesions (34,103), or by drugs such a *p*-chlorophenylalanine, metergoline, cyproheptadine, or methysergide (32,34,104). Consequently, there would be no reason to expect appreciable improvement in self-stimulation performance in response to 8-OH-DPAT if the stimulant effect of this compound were mediated simply by dampening central 5-HT release. However, stimulant effects produced by facilitation of DA transmission should be reflected by clear enhancement of self-stimulation.

Herberg and colleagues (110) put these arguments to the test by determining the effects on self-stimulation of 8-OH-DPAT administered in a wide range of doses, including low doses thought to act in a specific manner on presynaptic 5-HT_{1A} receptors (46). Rats were implanted with electrodes aimed at the midlateral hypothalamus and trained to operate a lever to obtain a 0.5 s threshold constant-current reinforcing stimulus on a VI 10-s schedule. Variable-interval responding for threshold stimulation occurs at approximately half the maximal response rate as determined by rate-intensity studies (137), and is maximally sensitive to small changes in central dopaminergic activity. The relatively slow rate of responding is also well within the rat's physical capacity, and is minimally sensitive to performance-related variables (101).

8-OH-DPAT had a biphasic effect on self-stimulation performance. At the lowest dose tested (3.0 μg/kg) there was a significant facilitation, but at higher doses (100–300 μg/kg) there was a depression of responding. The facilitatory effect lasted throughout the 1-h test period, but the depressions caused by higher doses were limited to the first 30 min of testing. Inspection of the rat during self-stimulation, and during periods of interrupted responding, revealed no signs of tremor, wet-dog shakes or other symptoms of the 5-HT motor syndrome (72), a condition previously shown to be associated with impaired self-stimulation (79).

The biphasic effect of 8-OH-DPAT on self-stimulation resembled its reported effect in other behavioral models, including male sexual behavior (3), conflict behavior (53), place preference (126), and feeding (44). This wide range of effects, involving an assortment of consummatory and nonconsummatory activities with little in common, suggests that the tendency of 8-OH-DPAT to promote feeding is not a specific action by 8-OH-DPAT on hunger mechanisms, but rather a consequence of nonspecific motivational arousal, as seen typically with agents causing dopaminergic stimulation.

Although 8-OH-DPAT can act directly on the DA receptor, it only does so in much higher concentrations that those reported to enhance feeding and self-stimulation performance (148). Moreover the direct action of 8-OH-DPAT on DA receptors may be selective for D_2 receptors (2,14), whereas self-stimulation requires both D_1 and D_2 activity (118). Thus, direct stimulation of the DA receptor does not seem a likely explanation for the enhancement of self-stimulation by low doses of 8-OH-DPAT. It is more likely that the low dose facilitation of self-stimulation is a result of disinhibition of DA transmission that is a secondary effect of reduced central 5-HT transmission. The depressant effect of higher doses of 8-OH-DPAT probably stems from their effects of postsynaptic 5-HT receptors (43) because there is ample evidence of impaired self-stimulation responding if 5-HT transmission is abnormally increased (12,79,93).

5-HT_3 Receptor Mediation of Drug-Induced Changes in DA Transmission

Mapping of the distribution of 5-HT_3 receptors indicates that they are abundant in terminal areas of central dopamine pathways (95). Moreover stimulation of these receptors by 5-HT_3 agonists facilitates DA release in the striatum (9) and accumbens (17,90), thus providing a neural substrate for interactions between 5-HT and DA systems. Interestingly 5-HT_3 an-

tagonists do not reduce the basal output of DA or its metabolites (15,75), but they do prevent the enhancement of DA release normally produced by a number of other drugs including morphine, nicotine, ethanol, and haloperidol (15). Amphetamine, however, is a notable exception because facilitation of DA release by amphetamine is not prevented by 5-HT_3 antagonists (15). Findings such as these provoked a great deal of interest in the possible clinical uses of 5-HT_3 antagonists in disorders where DA has been implicated, including schizophrenia and drug addiction (29,153,164), although so far their use is limited to antiemesis (104,154).

Behavioral studies have produced parallel findings to the original neurochemical studies: treatment with 5-HT_3 antagonists inhibits hyperactivity elicited by the neurokinin analogue, DiMe-C7 (74) and prevents the acquisition of habits conditioned to morphine, nicotine, phencyclidine, picrotoxin, or naloxone (1,16,84), but is ineffective against amphetamine (16) or cocaine (127,129).

Carboni and colleagues (15,16) have proposed an explanation for the peculiarly selective effectiveness of 5-HT_3 antagonists. They suggest that amphetamine and cocaine, which do not produce an increase in firing of the dopaminergic neurone, act directly on the DA synapse by displacing DA from synaptic terminals or by inhibiting synaptic reuptake, and that there is no role for 5-HT_3 receptors in these mechanisms. On the other hand, the dopaminergic effects of drugs like morphine and nicotine depend on intact transmission at excitatory 5-HT_3 receptors, presumably located presynaptically on DA neurons. The proposed serotonin–dopamine connection is normally quiescent under basal conditions, but when activated, increases dopaminergic firing. This account is supported by electrophysiological and neurochemical evidence, but a difficulty arises from findings that appear to show that 5-HT_3 antagonists, while sparing the discriminative properties and rewarding properties of cocaine and amphetamine (16,127,129), do block the locomotor stimulant and exploration-inducing properties of these drugs (27,155,156). These latter findings are difficult to reconcile with the proposed presynaptic action of 5-HT_3 antagonists, so the precise effects of 5-HT_3 antagonists on DA transmission are uncertain.

Intrigued by the apparent differential effectiveness of 5-HT_3 antagonists to block the behavioral responses to drugs that increase dopaminergic firing, but not the majority of behavioral responses to drugs like amphetamine and cocaine; and skeptical about the ambitious claims made for the potential therapeutic uses of 5-HT_3 antagonists, we decided to investigate the role of 5-HT_3 receptors in the behavioral responses to caerulin (a cholecystokinin analogue) and nicotine.

Do 5-HT_3 Receptors Mediate the Effects of Caerulin on Self-Stimulation Responding?

Cholecystokinin (CCK) is a neuropeptide occurring abundantly in the gut and brain. When administered systemically, CCK suppresses both feeding and spontaneous locomotor activity, but whether these effects reflect physiological satiety or a nonspecific consequence of nausea precedent to vomiting has been disputed (35,68). Ordinarily it might be expected that the behavioral consequence of drug treatments that cause aversive gastrointestinal effects could be avoided by treatment with conventional antiemetic agents. However, antiemetic drugs such as metoclopramide and domperidone are themselves antidopaminergic agents and produce behavioral depression in their own right. This situation is complicated further by the facts that CCK is rapidly degraded, produces rapid tolerance, and enters the brain with difficulty (30). We tackled these problems (78) by using self-stimulation to monitor the minute-by-minute changes in responding for self-stimulation produced by the relatively stable CCK analogue caerulin, and used ondansetron, a 5-HT_3 antagonist, for its potent antiemetic and antinausea properties (27,105).

A dose–response study revealed no effect of ondansetron (1–1000 μg/kg) on responding for self-stimulation on a variable interval 10-s (VI 10-s) schedule in rats equipped with an electrode implanted in the lateral hypothalamus (78). Similar results have been reported by others using electrodes aimed at either the lateral hypothalamus (51,69) or the ventral tegmental area (73). These finding are interesting because it is known that self-stimulation responding depends on a noncatecholaminergic descending pathway that causes release of dopamine by downstream dopaminergic neurones (8), so the lack of effect of ondansetron rules out any mediating role for 5-HT_3 receptors in this mechanism. Furthermore, the lack of effect of ondansetron in this and other behavioral models (155,163) indicates that in untreated rats 5-HT_3 receptors are functionally quiescent, and that the motivational effects of 5-HT_3 blockers do not depend on suppression of basal 5-HT activity at the 5-HT_3 receptor.

Caerulin (30 μg/kg), unlike ondansetron, produced an 82% reduction of self-stimulation responding in the 10 min following injection, and response rates returned to control levels over the next 50 min (78). Using a dose of ondansetron (100 μg/kg) that has been found effective in other drug-interaction studies on self-stimulation (111) we failed to detect any effect of ondansetron on the caerulin-induced reduction in self-stimulation responding. These results ruled out any role for the 5-HT_3–dependent mechanism associated with the vagus and area postrema in the depression of behavior by CCK and its analogues. Furthermore, studies employing the behavioral satiety sequence have provided strong support for the suggestion that CCK B receptor antagonists enhance food intake and postpone satiety (48), and thus argue against an explanation of CCK hypophagia in terms of nausea.

The Motivational Effects of Nicotine

Apart from the recreational use of tobacco, there is a good deal of evidence suggesting that nicotine has reinforcing or motivational properties. For example, nicotine's ability to release mesolimbic dopamine (39) is shared by almost all known addictive drugs (37,38), and mesolimbic dopaminergic activity is associated with reinforcing stimulation and motivated behavior (168). However, inspection of the literature relating to the reinforcing or motivational properties of nicotine reveals a good deal of conflicting evidence. Self-injection studies should shed light on reinforcement processes, but attempts to establish nicotine self-administration in various species have failed or indicated weak and unreliable effects (77,91). However, others, using reinforcement schedules that restrict the amount of nicotine injected, have shown robust self-administration (25,149), and it might be that a nonmonotonic dose–response relationship accounts for some of this variability (150).

Conditioned place preference (CPP) is a standard measure of the rewarding properties of a drug and yet, as with self-administration, consistent CPPs have proven difficult to demonstrate: nicotine has failed to reinforce position habits (19) with the same dose (0.8 mg/kg) that has been reported to produce maximal reward (64) and maximal place aversion (91). Schedule-controlled responding may provide a more sensitive

measure of nicotine's motivational effects. However, nicotine-treated rats responding for water on a variety of schedules have been reported to show erratic and nonsignificant changes, and significant depression followed by significant facilitation (115). In later operant studies using a variety of schedules (FR 15, VI 15), various rewards (water, sweetened milk, or food pellets) and a range of doses (0.25–1.6 mg/kg) all failed to show increased responding (41,138,158).

Self-stimulation studies, using preference measures or continuous reinforcement schedules, have shown enhanced responding or lowered stimulation thresholds (23,50,120,133), but other investigations using a variety of measurement techniques, have yielded ambiguous results (123,147).

In addition to the complications resulting from a nonmonotonic dose–response relationship there is strong evidence that nicotine can induce both tolerance (138,151), and a progressive enhancement in consecutive sessions (97,124) and biochemical studies have indicated an increase in nicotine-receptor number after repeated injections (97,146).

It seemed that what was needed to clarify these contradictory findings was a technique to monitor the behavioral response to nicotine both within and across sessions and over a range of doses. Schedule-controlled responding has long been established as a sensitive tool for analyzing the behavioral effects of drug treatments (36), although the time course of drug effects can be complicated by developing satiation for the reinforcer: with food and water rewards developing satiation might mask or exaggerate time-dependent changes in drug effects. However, this drawback is not shared by schedule-controlled responding for brain stimulation, because brain stimulation does not produce satiation. Furthermore, under appropriate conditions, self-stimulation of the hypothalamus and other brain stem sites is very sensitive to compounds affecting dopaminergic transmission [e.g., (66,136)], so tracking of schedule-controlled responding for self-stimulation should provide a convenient way to monitor dopaminergic effects of drugs, like nicotine, that are known to affect both dopaminergic transmission and behavior (110,168). Tracking the effects of nicotine on schedule-controlled responding for self-stimulation provided a clearer indication of the precise conditions under which nicotine administration leads to reinforcing effects (81) and enabled us to determine whether the 5-HT_3 receptor plays a significant role in mediating the behavioral response to nicotine (111).

Using ICSS Responding to Track the Effects of Acute and Chronic Nicotine Treatment

In rats trained to operate a pedal for threshold-current variable-interval stimulation of the midlateral hypothalamus, acute treatment with nicotine resulted in both dose- and time-dependent changes in responding (81). In the first 10 min after injection responding was unaffected by low doses of nicotine (40–130 μg/kg); but at 400 μg/kg, nicotine produced a marked depression of responding (see Table 3). This phase was followed by a prolonged dose-dependent facilitation [except for the highest dose tested (1.3 mg/kg), which caused prostration]. When the dose response study was repeated after chronic exposure to nicotine (400 μg/kg × 10 at 2–5-day intervals) the initial depressant effect was reduced and subsequent responding was enhanced, but only in the early minutes after injection (see Table 3). This latter effect suggests that the apparent sensitisation to chronic nicotine primarily depends on tolerance to its depressant effects, rather than on receptor upregulation. Both stimulant and depressant effects of acute nicotine were prevented by pretreatment with the centrally acting antagonist, mecamylamine (2.0 mg/kg), but not by the peripheral antagonist, hexamethonium (1.0 mg/kg) (see Table 3). Mecamylamine alone did not affect self-stimulation, indicating that although a nicotine-DA connection

TABLE 3

EXPERIMENTAL DETAILS AND RESULTS FOR STUDIES INVESTIGATING THE EFFECTS OF NICOTINE (Nic) AND ONDANSETRON ON RESPONDING FOR INTRACRANIAL SELF-STIMULATION AND INTERACTIONS WITH MECAMYLAMINE (MECAMYL), HEXAMETHONIUM (HEXAMETH), AND AMPHETAMINE (AMPHET)

Drug Treatment	Acute or Chronic	Pretreatment Drug	Nature of Effect or Interaction
Nicotine 40–400 μg/kg	Acute	None	130 μg/kg: weak delayed stimulation 400 μg/kg: initial depression followed by delayed stimulation
Nicotine 40–400 μg/kg	Chronic	None	40 and 130 μg/kg: stimulation 400 μg/kg: reduced initial depression followed by advanced stimulation
Nicotine 400 μg/kg	Subchronic	Mecamyl 2.0 mg/kg	Blocked both the stimulant and depressant effects of nicotine
Nicotine 400 μg/kg	Subchronic	Hexameth 1.0 mg/kg	Blocked neither the stimulant nor depressant effects of nicotine
Ondansetron 1–1000 μg/kg	Acute	None	No change
Ondansetron 100 μg/kg	Acute	Amphet 500 μg/kg	The stimulant effect of Amphet was unchanged by ondansetron
Ondansetron 100 μg/kg	Acute	Acute Nic 400 μg/kg	The depressant effect of nicotine was reduced by ondansetron
Ondansetron 100 μg/kg	Acute	Chronic Nic 400 μg/kg	The depressant effect of nicotine was eliminated by ondansetron

[probably dependent on somatodendritic or terminal presynaptic cholinoreceptors that facilitate mesolimbic DA release (39,139)] might modulate self-stimulation performance, it is not crucial for self-stimulation.

The initial depressant effect of nicotine has frequently been seen in studies of operant behavior and locomotor behavior [e.g., (20–22,115,116)], but the mechanism underlying these effects are uncertain. However, similar depressions of self-stimulation responding have been reported following treatment with aversive drugs like picrotoxin or anxiogenic β-carbolines (83,128); and the induction of a brief aversive state by an injected bolus of nicotine could account for many failures to establish positive CPPs (19,91) or to establish nicotine self-administration [reviewed in (77)]. Where nicotine self-administration has been established, the amount of drug injected was sharply restricted (25,149), in keeping with our finding that low doses of nicotine do not depress self-stimulation (81).

Nicotine is unusual among stimulant drugs in being consistently subject to tolerance and sensitization in its effects on self-stimulation, especially as both processes are found in the same test procedure with a single dose. Upregulation of nicotinic receptors has been proposed as an explanation for sensitzation to nicotine (76), but our results (81) appear to be better explained by the proposal that tolerance develops only to the depressant effects of nicotine, and as this wanes, a facilitation is unmasked (116).

The Role of the 5-HT$_3$ Receptor in Mediating the Behavioral Responses to Direct and Indirect Stimulants of DA Transmission

Having established the effects of nicotine on responding for ICSS, we then went on to investigate the role of 5-HT$_3$ receptors in mediating the effects of direct and indirect stimulants of DA transmission (111).

Direct stimulation of DA transmission was established using a modest dose of amphetamine (0.5 mg/kg) that produced a 60% increase in responding for self-stimulation through electrodes implanted in the midlateral hypothalamus. This level of responding was completely unaffected by pretreatment with ondansetron (100 μg/kg) (see Table 3), a finding that is in agreement with other studies that have failed to find any effect of ondansetron or other 5-HT$_3$ antagonists in tests of amphetamine-reinforced place preference (16) amphetamine-induced release of mesolimbic DA (15), or cocaine-induced locomotor activity or reinforcement (127,129). All of these results support the suggestion that 5-HT$_3$ antagonists do not antagonize drugs that act directly on the DA synapse (15,16).

Indirect stimulation of DA transmission by nicotine (400 μg/kg) again produced a biphasic effect: an initial depression, followed by an enduring moderate facilitation. Pretreatment with ondansetron (100 μg/kg) attenuated or reversed the initial depression of responding, but the ensuing facilitation was unaffected (see Table 3). Like those of amphetamine and cocaine, the stimulant effects of nicotine depend on increased mesolimbic DA transmission (18,124), but the nicotine effect differs by being dependent on increased DA neuronal firing. According to Carboni et al. (15,16) the DA firing provoked by nicotine (and other indirect stimulants of DA transmission) is mediated by an interpolated 5-HT$_3$ receptor. The effects of nicotine on self-stimulation should, therefore, be under the inhibitory influence of ondansetron. The present results support this prediction, but only in part. The attenuation by ondansetron of the initial depressant effect of nicotine is in agreement with the proposal by Carboni and colleagues (15,16), but the failure of ondansetron to influence nicotine's facilitation of responding is less easily explained. It might be that the facilitatory and depressant effects of nicotine reflect two pharmacologically distinct effects, one blocked by ondansetron, the other not. However, both effects of nicotine are blocked by the nicotine antagonist, mecamylamine (81), so any dissociation of these effects would have to occur downstream from the nicotine receptor. An alternative possibility is that the duration of nicotine's initial depressant effect is limited by the developing facilitatory effect so that an ondansetron-induced reduction in the initial depression would unmask the full extent of nicotine's stimulant activity; this would counteract the putative antistimulant effect of ondansetron. If this is the case, then our results with ondansetron are entirely compatible with its proposed ability to block nicotine's rewarding properties (16).

The Role of 5-HT$_2$ Antagonism in the Clinical Superiority of Atypical Neuroleptics

The recently introduced atypical neuroleptics have been differentiated from the more established typical neuroleptics according to their biochemical and clinical effects (96). Atypical neuroleptics appear to be clinically superior, first because they are effective in treating both positive and negative symptoms of schizophrenia, even in patients refractory to conventional treatments; and second, because they are relatively free from extrapyramidal side effects (EPS) (92). Comparisons of pharmacological profiles reveal that typical neuroleptics tend to be relatively selective antagonists at D_2 receptors, whereas atypical neuroleptics show greater affinities for other sites (including 5-HT$_2$ and α_2-receptors) that might contribute to their therapeutic advantages (100,121).

Neuroleptic-induced improvements in positive symptoms are thought to result from antagonism of D_2 receptors in the mesolimbic DA pathway (71), while EPS result from D_2 antagonism in the nigrostriatal DA pathway (56). Consequently, the proposal that atypical neuroleptics act preferentially on the mesolimbic system (165) might contribute to an explanation of their relative freedom from EPS. However, the affinity of atypical agents for the D_2 receptor shows marked variability: risperidone, like conventional neuroleptics, is a potent D_2 blocker, but clozapine has relatively low affinity for the D_2 receptor (100), suggesting that some other aspect of their pharmacological profiles might contribute to their clinical efficacy.

Evidence supporting an important role for 5-HT$_2$ antagonism includes the ability of ritanserin, a potent 5-HT$_{2/2c}$ antagonist with relatively low affinity for the D_2 receptor (100), to reduce neuroleptic-induced EPS (7). Preclinical studies indicate that the cataleptic response to D_2 antagonists (which is mediated by the nigrostriatal DA system) is reduced by coadministration of 5-HT$_2$ antagonists, suggesting that 5-HT$_2$ antagonists reduce the effects of D_2 antagonists in the nigrostriatal DA system [(6,161), but see also (160)]. The effects of 5-HT$_2$ antagonism on D_2-mediated transmission in the mesolimbic system are less certain: clozapine ameliorates the positive symptoms of schizophrenia, but is a relatively weak D_2 antagonist (100), so it seems unlikely that its 5-HT$_2$ antagonist properties further reduce its ability to antagonize D_2 transmission in the mesolimbic DA pathway. Consequently, we sought to determine how coadministration of ritanserin affected the behavioral effects of raclopride (a D_2/D_3 antagonist).

TABLE 4

EXPERIMENTAL DETAILS AND RESULTS FOR STUDIES INVESTIGATING THE EFFECTS OF RITANSERIN ON RACLOPRIDE-INDUCED CHANGES IN CONSUMPTION OF VARIOUS SUCROSE (suc) SOLUTIONS, AND THE EFFECTS OF DOI ON RECOVERY FROM RISPERIDONE-INDUCED DEPRESSION OF RESPONDING FOR INTRACRANIAL SELF-STIMULATION (ICSS) FROM ELECTRODES IMPLANTED IN THE VENTRAL TEGMENTAL AREA (VTA)

Drug Treatment (mg/kg)	Reinforcer	Pretreatment Drug	Test Duration (min)	Nature of Effect or Interaction
Raclodpride (0.15, 0.30)	Sucrose (0.7, 7, 34%) + water	None	60	0.15 mg/kg: no effect 0.30 mg/kg: increased intake of 0.7 and 7% suc; no effect on 34% suc.
Ritanserin (0.1–0.4)	Sucrose (0.7, 7, 34%) + water	None	60	No effects at any dose
Raclopride (0.15)	Sucrose (0.7, 7, 34%) + water	Ritanserin (0.4)	60	Reduced intake of 7% suc Increased intake of 34% suc
Risperidone (0.03–0.9)	VTA ICSS	None	60	Dose-dependent depression of responding
Risperidone (0.2, 0.9)	VTA ICSS	None	120	Depression followed by complete (0.2) or partial (0.9) recovery
Risperidone (0.9)	VTA ICSS	None	210	Depression followed by complete recovery
DOI (0.24–2.4)	VTA ICSS	None	60	Dose-dependent depression
Risperideone (0.9)	VTA ICSS	DOI (0.8)	240	Recovery from effects of Risp unaffected by DOI

5-HT_2/D_2 Interactions as Revealed by Tests of Sucrose Consumption

In untreated rats the sucrose concentration-intake function is an inverted-U shape with an intermediate (~7%) concentration supporting the greatest intake (113). Although intake of very sweet solutions is reduced, they are not aversive because preference tests reveal that very sweet solutions are reliably preferred over less sweet solutions (131). Developing satiety can also be ruled out as an explanation because differences in intakes of 7 and 34% sucrose are apparent within the first 5 min of access. Rather, it seems that very intense rewards saturate the brain mechanisms mediating reward so that further rewards produced by increased responding become superfluous (108).

In two-bottle tests with water as the alternative, treatment with raclopride shifts the concentration-intake function to the left, so that intake of concentrations from the ascending limb is reduced and intake of concentrations from the descending limb is increased (131). Because neuroleptics do not affect the ability to discriminate sucrose concentration (166), it appears that they blunt the rewarding properties of sweet solutions (67,170).

Using the same two-bottle test methodology we found that 0.15 mg/kg raclopride had no effect on sucrose intake. However, when the dose of raclopride was doubled, intakes of sucrose concentrations from the ascending limb of the concentration–intake curve (0.7 and 7%) were reduced, but intake of 34% sucrose was relatively unaffected. When tested alone, ritanserin (0.1–0.4 mg/kg) had no effect on sucrose intake regardless of concentration; however, when ritanserin (0.4 mg/kg) was given in combination with raclopride (0.15 mg/kg) intake of 7%, sucrose was reduced and intake of 34% sucrose was increased (see Table 4). From these results it appears that ritanserin potentiated the effects of raclopride on sucrose consumption (112).

Similar effects to those of systemic raclopride have been found using intracerebral injections of the D_2/D_3 antagonist sulpiride into the nucleus accumbens or anterodorsal striatum (132): intake of sucrose concentrations from the ascending limb of the concentration–intake curve was reduced, but intake of concentrations from the descending limb was increased. It seems unlikely that the potentiation of raclopride by ritanserin is mediated by the anterodorsal striatum because D_2 antagonist-induced catalepsy (which is dependent on nigrostriatal DA) is reduced rather than potentiated by 5-HT_2 antagonists [(6,161), but see (157,160) for discrepant results]. However if 5-HT_2 antagonism potentiates the effects of D_2 antagonism in the mesolimbic DA system, it might explain why a drug like clozapine with relatively weak affinity for D_2 receptors is clinically effective, but less prone to produce EPS.

Schedule-Controlled Behavior as a Means for Distinguishing Between Typical and Atypical Neuroleptics: The Role of 5-HT_2 Antagonism

Operant behavioral studies in rats have provided another means for distinguishing between typical and atypical neuroleptics. It is well established that conventional neuroleptics produce an extinction-like decrement in responding, culminating in a prolonged reduction of responding. This occurs when the start of testing is delayed to allow for drug uptake, and is apparent in both appetitively and aversively motivated tasks, including ICSS (61,143). Atypical neuroleptics, on the

other hand, produce a relatively stable inhibition of responding throughout the duration of short test sessions (144). This difference raises the possibility that operant responding might provide a fruitful technique for determining which aspect of the complex pharmacological profile of atypical neuroleptics accounts for their behavioral differences from typical neuroleptics. If it is the 5-HT_2 antagonist properties (106), then coadministration of a 5-HT_2 agonist should cancel the differences; if it is the α_2 antagonist properties (121), then coadministration of an α_2 agonist should cancel the difference.

We decided to employ this strategy using variable interval responding for ICSS from electrodes implanted in the ventral tegmental area (the origin of the mesolimbic DA pathway) as the operant response. Our first dose–response study tested the effects of the atypical neuroleptic, risperidone of self-stimulation responding in a 1-h session, starting immediately after drug administration. The results revealed dose-dependent extinction-like reductions in responding reflecting drug uptake, with doses of 0.3 and 0.9 mg/kg inhibiting responding by more than 50% (74). However, the depression of responding following treatment with 0.3 mg/kg risperidone appeared to be showing signs of recovery within 1 h of treatment—a time at which receptor occupancy is still virtually complete (152). Further investigations, using longer test periods and time-outs confirmed total recovery from the depressant effects of 0.2 mg/kg risperidone within 2 h of injection. Even a dose (0.9 mg/kg), which produced almost total depression of responding, showed significant recovery within 2 h (see Table 4). Furthermore, this recovery of responding was independent of the opportunity to engage in responding, indicating that recovery was not a learned coping response. Rather, it seems that the depressant activity of risperidone is self-limited, suggesting that atypical neuroleptics contain their own antidote to the incremental inhibitory activity exhibited by typical neuroleptics. Direct comparisons of the time courses of the depressions of responding caused by typical and atypical neuroleptics confirm that, even when the magnitude of the initial depression is equated, atypicals (clozapine and risperidone) produce a transient depression, whereas responding depressed by typicals (haloperidol and chlorpromazine) shows little sign of recovery 4 h after injection (see Table 5) (Montgomery et al. submitted).

The possibility that the recovery of self-stimulation from depression produced by atypical neuroleptics was due to their 5-HT_2 antagonist properties was tested by attempting to prolong the depressant effects of risperidone by coadministration of the 5-$HT_{2/2C}$ agonist, DOI (see Table 4). When given alone, DOI depressed self-stimulation responding, but it nevertheless failed to prolong the depressant effects of risperidone; indeed, the time course of risperidone's effects was unaltered by DOI (74). Rather than DOI antagonizing the recovery from response inhibition, risperidone appeared to counteract the response–depressant effects of DOI.

A similar failure to eliminate differences between the behavioral effects of typical and atypical neuroleptics has been reported (145). In rats responding on a fixed-ratio schedule for food, typical neuroleptics produced an incremental inhibitory effect on responding (i.e., within session response decrements) that contrasted with a stable inhibition of responding found after treatment with atypical antipsychotics (144). Arguing that differences in the affinities of these drugs for 5-HT_2 receptors might explain their differential behavioral effects, an attempt was made to counteract the incremental effects of haloperidol by coadministering the 5-HT_2 antagonist ritanserin (145). On its own, ritanserin had no effect on response rates, and in combination with haloperidol, the incremental inhibition of responding was potentiated rather than antagonized. These results are similar to those where ritanserin failed to alter sucrose consumption, but potentiated the effects of raclopride (112). It seems clear that the behavioral effects of neuroleptic drugs can be modulated by 5-HT_2

TABLE 5

EXPERIMENTAL DETAILS AND RESULTS FOR STUDIES INVESTIGATING THE EFFECTS OF CLOZAPINE, RESPERIDONE, HALOPERIDOL, AND CHLORPROMAZINE (CPZ) ON RESPONDING FOR INTRACRANIAL SELF-STIMULATION (ICSS) FROM ELECTRODES IMPLANTED IN THE VENTRAL TEGMENTAL AREA (VTA) AND INTERACTIONS WITH IDAZOXAN AND CLONIDINE (Clon)

Drug Treatment (mg/kg)	Pretreatment Drug	Test Duration (min)	Nature of Effect or Interaction
Clozapine (3.0, 6.0)	None	60	Dose-dependent depression of responding
Clozapine (6.0)	None	240	Initial 70% depression, followed by complete recovery
Risperidone (0.3)	None	240	Initial 70% depression, followed by complete recovery
Haloperidol (0.075)	None	240	Initial 70% depression, followed by continued depression
CPZ (1.0)	None	240	Initial 70% depression, followed by continued depression
Clon (0.015)	Risperidone (0.9)	210	Clon prolonged the Risperidone-induced depression
Idazoxan (0.3–3.0)	None	60	3 mg/kg: 40% depression, followed by complete recovery
Clozapine (6.0)	Clon (0.015)	240	Clon prolonged the clozapine-induced depression
CPZ (1.0)	Idazoxan (3.0)	240	Idazoxan curtailed the CPZ-induced depression

antagonists, but this interaction does not explain the differing behavioral responses to typical and atypical neuroleptics.

The Role of α_2 Antagonism in the Behavioral Effects of Atypical Neuroleptics

In view of our failure to implicate the 5-HT_2 antagonist properties of atypical neuroleptics in their unusually brief response–depressant effects, we turned to our alternative hypothesis: α_2 antagonism.

A dose–response study confirmed that clonidine causes a dose-dependent depression of self-stimulation with a modest 15% inhibition after a dose of 0.015 mg/kg (63,82). This dose was given to rats as they were recovering from the response–depressant effects of risperidone (0.9 mg/kg). The inhibition of responding caused by risperidone was maximal 60–120 min after injection, followed by progressive recovery to within 15% of baseline levels 90 min later. When clonidine was injected 150 min after injection of risperidone the recovery of responding was interrupted (see Table 5). This interruption of recovery could not be explained by simple additivity of the effect of clonidine because the inhibition caused by clonidine was too small and did not increase with time (80). This point was later reinforced when clonidine (0.015 mg/kg) was given at the same time as clozapine (6 mg/kg) and responding was tested 30–60 and 180–240 min later (see Table 5). Under these circumstances, there was no overall effect of clonidine when given alone, but it did substantially retard recovery from the inhibitory effects of clozapine (see Fig. 1) (Montgomery et al., submitted). These results suggest that at least one 'atypical' feature of risperidone and clozapine (the transient depression of self-stimulation responding) depends on their affinity for the α_2-adrenoceptor, as previously proposed (121). Moreover, the resulting curtailment of their behavioral inhibition might equally account for their relative freedom from extrapyramidal side effect in the clinic.

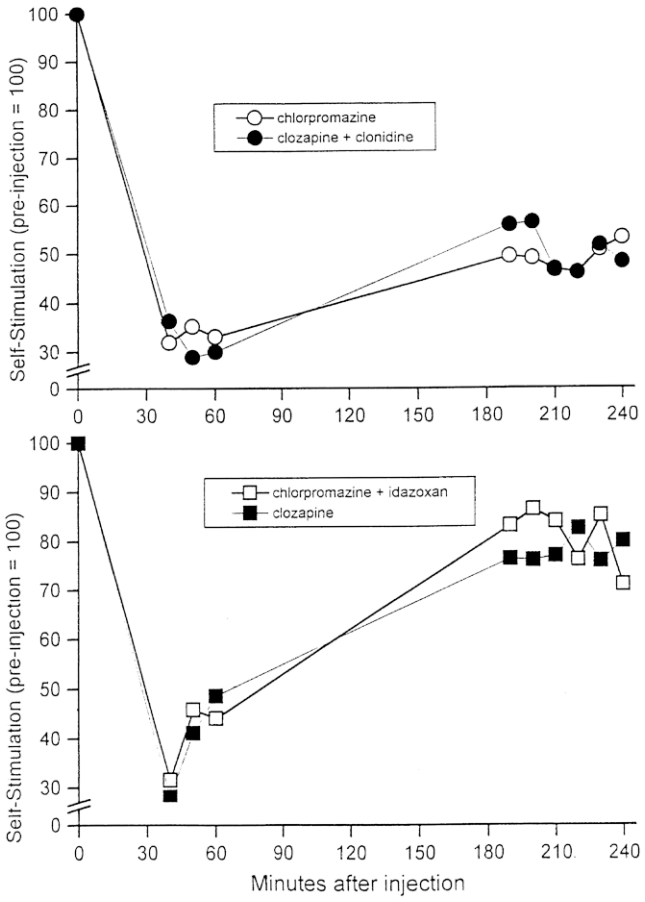

FIG. 1. Comparisons of the response depressant effects chlorpromazine (1.0 mg/kg) and clozapine (6.0 mg/kg) + clonidine (0.015 mg/kg) (upper panel), and clozapine (6.0 mg/kg) and chlorpromazine (1.0 mg/kg) + idazoxan (3.0 mg/kg) (lower panel) on responding for self-stimulation on a VI 10 schedule. Test sessions were preceded by a warm-up period of approximately 40 min, the last 30 min before injection providing a predrug baseline. Electrodes were implanted in the ventral tegmental area and neuroleptic doses were chosen to produce equivalent intital depressions of responding. Response rates are expressed as a percentage of preinjection baselines, and all points are means.

Having demonstrated that the unusually abbreviated inhibitory effects of atypical neuroleptics can be counteracted by treatment with an α_2 agonist, it occurred to us that it would be more appropriate to establish whether the more prolonged effects of typical neuroleptics could be curtailed by coadministration of an α_2 antagonist. We did this by testing the effects of idazoxan on responding depressed by chlorpromazine (Montgomery et al., submitted) (see Table 5).

A dose–response study revealed that 3 mg/kg idazoxan produced a short-lasting inhibition of self-stimulation responding: its maximal effect was a 40% reduction in responding 30 min after injection; by 1 h response rates had returned to baseline levels. When tested in combination with chlorpromazine, the effect of idazoxan was clear: 180–240 min after treatment with chlorpromazine responding was approximately 50% of the baseline rate, but under the idazoxan–chlorpromazine condition responding had recovered to over 80% of the baseline rate (see Fig. 1).

Encouraged by these results we then investigated the role of α_2-adrenoceptors in the differential response decrement patterns of typical and atypical neuroleptics on FR10 responding for food (144,145). Haloperidol produced the expected extinction-like incremental inhibition of responding, and clozapine produced a stable inhibition of responding throughout the test session (see Table 6). However, the addition of idazoxan to haloperidol did not produce a clozapine-like pattern of responding, and the addition of clonidine to clozapine did not produce a haloperidol-like incremental inhibition of responding (109). Consequently, there is no evidence that either the 5-HT_2-antagonist (145) or the α_2-antagonist properties of atypical neuroleptics explain differences between the response decrement patterns of typical and atypical neuroleptics.

Taken together, these results clearly indicate that different neural mechanisms are involved in the changes in patterns of operant responding resulting from treatment with typical and atypical neuroleptics (i.e., response decrement patterns and time-dependent recovery from response inhibition). The depression of operant responding by neuroleptics has been explained in terms of either motor or motivational/incentive processes. Although both points of view are supported by empirical evidence, it is clear that incremental inhibitory effects are found with both appetitively and aversively motivated and unconditioned behaviors [reviewed in (62)]. This would appear to argue in favor of a performance-related deficit, especially as microanalysis of response decrement patterns reveals a slowing of response termination that cannot be mimicked by reductions in reinforcement magnitude (55).

TABLE 6

EXPERIMENTAL DETAILS AND RESULTS FOR STUDIES INVESTIGATING THE EFFECTS OF HALOPERIDOL AND CLOZAPINE ON FIXED RATIO (FR 10) RESPONDING FOR FOOD AND THEIR INTERACTIONS WITH IDAZOXAN AND CLONIDINE (Clon)

Drug Treatment (mg/kg)	Pretreatment Drug	Test Duration (min)	Nature of Effect or Interaction
Haloperidol (0.03, 0.10)	None	15	0.03 mg/kg: extinction-like incremental depression of responding
Clozapine (1.0–9.0)	None	15	Stable depressions of responding
Haloperidol (0.03)	Idazoxan (1.0, 3.0)	15	Extinction-like incremental depressions of responding
Clozapine (3.0)	Clon (0.005, 0.015)	15	Stable depressions of responding

Our results with self-stimulation responding provide strong support for the suggestion that at least one behavioral effect that distinguishes between typical and atypical neuroleptics (the duration of inhibitory effect on self-stimulation responding) depends on their differing affinities for the α_2-adrenoceptor. How these results relate to clinical differences between typical and atypical neuroleptics is unclear, but the abbreviated effect of atypical neuroleptics on self-stimulation responding might be another expression of the mechanism that underlies the reduced propensity of atypical neuroleptics for extrapyramidal side effects. One possible explanation is that the ability of α_2-adrenoceptor antagonists to increase DA release in the striatum (122) offsets the effects of D_2 receptor blockade (121). Diminished extrapyramidal activity would not explain the improved efficacy of atypical neuroleptics in the treatment of otherwise drug-resistant psychotic symptoms (except possibly by enabling patients to tolerate higher doses and thereby ensuring more effective blockade of therapeutically relevant receptors). However, α_2-adrenoceptor blockade might be intrinsically therapeutic (121), as suggested by observations that idazoxan augments fluphenazine in schizophrenic patients (102), improves cognitive function in frontal lobe dementia (141) and increases mood (125).

CONCLUSIONS

This series of experiments enables a number of conclusions to be drawn. It is clear that studies of feeding behavior and responding for ICSS can detect interactions between DA and 5-HT systems, and that the precise nature of the interaction varies in accordance with the subtype of 5-HT receptor manipulated and the behavioral paradigm employed.

The agonist activity of 8-OH-DPAT at 5-HT_{1A} autoreceptors results in a disinhibition of DA transmission that produces changes to wood gnawing, food consumption, peripprandial behaviors, and responding for self-stimulation.

Activity at 5-HT_3 receptors mediates the effects of a variety of drugs that indirectly increase mesolimbic dopamine transmission, including the response–depressant effects of nicotine on self-stimulation responding.

Interactions between 5-HT_2-antagonists and D_2-antagonists are, however, less easily summarized because the nature of the interaction appears to vary, depending on the behavioral paradigm used. 5-HT_2 antagonists potentiate the effects of D_2 antagonists on sucrose consumption, and these effects appear to depend on blockade of the mesolimbic DA system. The cataleptic response to DA antagonists, on the other hand, depends on blockade of the nigrostriatal DA pathway, and this effect is opposed by coadministration of ritanserin. The problem arises in considering the effects of 5-HT_2-antagonists on within-session response decrements produced by typical neuroleptics: it has been reported that ritanserin potentiates haloperidol-induced within-session response decrements in lever pressing for food (145). Because similar response decrements also occur in aversively motivated responding, an explanation in terms of nigrostriatally mediated motor impairment rather than mesolimbic-mediated blunting of reward appears to be indicated. However, if neuroleptic-induced within-session response decrements depend on blockade of nigrostriatal DA receptors, ritanserin should be expected to counteract the effect.

Clarification of this problem requires further research, but evidence indicates that it is too simplistic to allocate neuroleptic-induced motor impairments to DA blockade in the nigrostriatal pathway and reward blunting to DA blockade in the mesolimbic pathway. For example, nucleus accumbens DA depletion or intraccumbens injection of neuroleptics cause changes in response output (in particular, there is a slowing of fast operant responding that contrasts with the effects of extinction) (142,143). Consequently, it appears that further studies, designed to provide a finer analysis of the roles played by the various projection areas of both the nigrostriatal and mesolimbic DA pathways in different behaviors, are required.

Finally, our data investigating the role of α_2-adrenoceptor antagonism in the unusually abbreviated depression of ICSS responding by atypical neuroleptics, provide strong support for the suggestion that at least one difference between the behavioral effects of typical and atypical neuroleptics is due to the α_2-adrenoceptor antagonist properties of the latter. This finding reinforces the value of ICSS responding as a unique means for investigating drug effects on behavior over long periods without the problems associated with developing satiety, and supports the suggestion that the α_2-adrenoceptor antagonist properties of atypical neuroletpics might contribute to their relatively low propensity for inducing EPS.

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