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SOCIOPHARMACOLOGY[1]

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INTRODUCTION

This review focuses on recent thinking and empirical findings in the field of sociopharmacology. We will present a paradigm that facilitates the identification, organization, and evaluation of sociopharmacological data. Selected findings relevant to the paradigm are then reviewed. This review is followed by a brief overview of the authors' studies in the field. Throughout the paper problems associated with research strategies and data interpretation peculiar to this field receive close attention.

BACKGROUND

Sociopharmacology began when investigators became convinced that it was necessary to assess the effects of pharmacological agents—primarily psychotropic agents—on the behavior and feelings of individuals in social settings. There were good and varied reasons for this interest: medications often were taken because of distressing symptoms associated with social interactions; social variables appeared to influence medication effects; the effects of many psychotropic agents could not be adequately evaluated outside of social settings; and self-report statements of the effects of drugs

were difficult to interpret. These reasons remain as cogent today as they did three and a half decades ago when the first studies in sociopharmacology began.

Investigations in sociopharmacology have involved animals from a variety of species and have developed primarily along two different lines. The first line has emphasized studies of the effects of one or more drugs on one or more members of a social group. Data from these studies reinforced what early investigators suspected, namely, that social variables (e.g. age and sex composition of the group, familiarity among group members) influenced responses to drugs. The second line of research has focused on physiological-biochemical profile differences. Social, physical environmental, and/or experiential variables impact the biochemical, physiological, and anatomical profiles of animals, and, in certain instances, specific profiles are associated with characteristic metabolic and behavioral responses to drugs. An important synthesis of these lines of research occurred when studies focused on the effects of drugs on animals of different social status. Findings not only showed status-related behavioral responses to equivalent doses of selected medications, but they also suggested that status differences were associated with distinct physiological and biochemical profiles.

As with most areas of investigation, what lay ahead was not fully apparent to the early investigators. After some 35 years of research, what is implied by the term "sociopharmacology" is now becoming apparent. And with this realization it has also become clear that sociopharmacology is a field desparately in need of a conceptual framework to order its findings and direct its future research. One such framework is presented in Figure 1.

Figure 1 is an idealized representation of the kinds of research questions which have been or might be asked with respect to interrelationships between (*a*) social and physical environmental variables, (*b*) biochemical and physiological states, and (*c*) pharmacological agents. The arrows do not necessarily represent the routes by which events are thought to occur in nature. For example, Routes *E–D* in sequence are the presumed paths of a pharmacological agent's effects on behavior. However, studies focusing

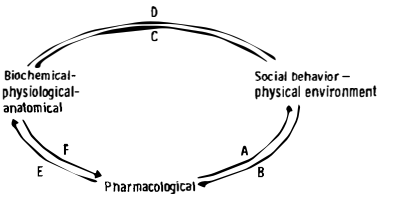

Figure 1 Diagrammatic representation of a paradigm for sociopharmacology. The figure is explained in text.

only on Route *A* can be conducted and, indeed, by far the majority of studies in sociopharmacology have focused on Route *A*. Conversely, Route *B* studies can be undertaken, although the presumed natural path is, serially, Routes *C–F*.

Figure 1 has both strengths and weaknesses. Its principal strength has already been mentioned: it provides organization for a diverse and complex field of investigation and suggests the kinds of relationships which require investigation. The major weakness inherent in Figure 1 is that it is incomplete. For example, among nonhuman species, a host of environmental variables such as light, temperature, nutrition, and available space interact with social variables to affect biochemical, physiological, and anatomical parameters. Genetic contributions to Figure 1 are not easily included in the figure because phenotypic characteristics result from interactions between genotype and the physical and social environments. Logical problems also exist: the category social behavior, for example, is not equivalent to the category pharmacological agent, which means there are limits to the specificity with which data can be interpreted. Further, social behavior is still poorly understood. We know that in selected instances, altering group composition alters drug responses in individual animals, but in most cases we have no idea why. Moreover, as yet we cannot accurately predict the drug responses of an animal who is living in a group whose composition has not been previously studied; that is, we have no theory of social organization which can be translated into statements about related biochemical and physiological states. Questions relating to social behavior are further complicated by the fact that kin and nonkin relate differently, and, among nonhuman primates, birth order may be of critical importance with respect to subsequent social status and physiological parameters. Species also differ, and generalizations about drug effects across species are problematic at best. Finally, studies of affective states are largely limited to humans.

Figure 1 also hints at the difficulty of conducting research in this field. For example, a drug might be given to a single group-living animal. Suppose the drug alters certain biochemical variables (Route *E*) which, in turn, alter the animal's behavior (Route *D*). The behavioral changes may then alter group behavior towards the effected animal, in which case Route *C* may become relevant and resulting biochemical-physiological changes may enhance or dampen subsequent Route E effects. We do not suppose such a complex chain to apply to all experimental situations, but the potential for complex interactions suggests that most findings will reflect a degree of influence by uncontrolled variables. Thus, it may be necessary to study effects of drugs across a variety of social conditions and to limit reports of drug effects to specific conditions. In studies reported below, for example, whole blood serotonin levels differ in dominant adult male vervet monkeys

not only as a function of isolate or group housing, but also as a function of the social composition of a group.

To our knowledge, no investigator(s) has attempted to explore all of the main routes shown in Figure 1. Further, only a few studies have been replicated. Moreover, species selected for research, the group composition of research subjects, the physical characteristics of research settings, and the control of possible influencing variables all have differed across studies. Thus, few generalizations are possible from current findings. In discussing findings, we generally have not included dose information, species name, or specified either the social or physical conditions under which studies were conducted. Where possible, findings relevant to routes are organized either in terms of (*a*) possible drug effects on behavior, (*b*) the relevance of animal models for testing clinically useful drugs, or (*c*) social behavior as an endpoint for drug studies. We have not undertaken a complete literature review. Rather, we have attempted to select studies illustrating the routes under discussion and areas of uncertainty or controversy. Finally, it will be clear that many of the studies selected to illustrate one route might also be used to illustrate another route.

FINDINGS

Route A (Figure 1): Pharmacological-Social Behavior Relationships: Or, The Effects of Pharmacological Agents on Social Behavior

The behavioral effects of benzodiazepines have received considerable attention. Salzman et al (1) found that chlordiazepoxide given to humans who were studied in small groups increases individual affective, but not behavioral, hostility. Diazepam has been shown to decrease self-disturbance behaviors and to moderately increase social behavior in rhesus monkeys reared in social isolation (2). In mice, however, acute but not chronic treatment with three benzodiazepines decreased social interactions (3). In group living golden hamsters, Poole (4) observed that chlordiazepoxide decreases aggression and defensive fighting while increasing investigative behavior [see also (5 and 6) for human studies]. Sepinwall et al (7) tested the effects of chlordiazepoxide and propranolol on conflict behavior in rats and found both dose and combination effects. And finally, Zwirner et al (8) injected male mice with chlordiazepoxide, chlorpromazine, pentobarbital, *d*-amphetamine, and YG-19-256 and found that different types of aggression and motor activity were associated with each drug.

The behavioral effects of a variety of stimulants have been studied. Using *d*-amphetamine, Bellarosa et al (9) demonstrated that low doses increase most social and interactive behaviors in stumptail monkeys, whereas high

doses reduce social interactions. In Gambill & Kornetsky's (10) studies with rats, subordinate animals treated with *d*-amphetamine withdrew from social interactions whereas dominant animals receiving the drug seemed oblivious to other animals (see also 11). In partial contrast to these findings, Heimstra (12) demonstrated that amphetamine-treated rats engage in more barrier directed behavior than saline-treated controls, and sniffing increased in solitary animals but decreased in animals in social groups. Using group living squirrel monkeys, Poignant and Avril (13) tested the behavioral effects of four drugs (amphetamine, piribedil, amitriptyline, and amineptine) and found both drug specific social behavior changes as well as different behavioral responses among dominant and subordinant animals. Whalen et al (14) have treated hyperactive boys with methylphenidate and placebo and found that the boys receiving placebo showed lower rates of task attention and an increase in the following behaviors: gross motor movement, regular and negative verbalization, noise making, physical contact, and social imitation.

A number of other psychotropic medications also have been the subject of a number of investigations. Syme & Syme (15) reported that group living rats treated with chlorpromazine were more sociable than animals treated with methamphetamine or isotonic saline. Miller et al (16) tested a battery of drugs on female rhesus monkeys and observed different responses: chlorpromazine dampened both the transmission and reception of nonverbal cues; amphetamine improved communication in cooperative conditioning; and phencyclidine (Sernyl) had minimal effects on these variables (see also 17). Using rats, File (18) has shown that chlorpromazine increased the latency with which animals started to explore a new environment and decreased the time spent exploring it. In studying subjects with psychiatric disorders, Gillis (19) has demonstrated that chlorpromazine impairs social cognitive functions independent of the complexity of the learning situation. Compared to saline-treated controls, imipramine-treated rhesus monkeys undergoing repeated separation show a significant behavior improvement over a time-course similar to that shown by humans who received this drug (20). Stewart (21) injected different numbers of group living rats with saline or scopalamine and demonstrated behavioral changes when all group members were treated with scopalamine, but few changes when only half the animals in a group were treated.

The effects of cannabis and cocaine have been investigated under a variety of experimental conditions. When delta-9-tetrahydrocannabinol was given to selected members of rhesus groups, animals moved closer together and distances became more variable (22). In communication studies, treated stimulus animals decreased their facial expression displays whereas responder animals developed an improved ability to discriminate stimulus ani-

mals' expressions (23). In small groups of humans, Salzman et al (24) have shown a decrease in hostile feelings in response to a frustrating stimulus when group members received delta-9-tetrahydrocannabinol. Using repeated cocaine injections in rhesus monkeys, Post et al (25) have shown that a variety of stereotypic responses develop. Levett et al (26) have demonstrated that cannabis, when given to adult female chacma baboons, sometimes results in social behavior or locomotion changes, but that these changes are highly influenced by physical environmental variables.

Drugs related to opiate receptors are increasingly a focus of investigation. For example, Meller et al (27) tested the effects of naltrexone on male talapoin monkeys and observed a decrease in sexual behavior, an increase in grooming behavior, and no change in aggression among males; testosterone, luteinizing hormone, and cortisol increased during treatment. Methadone treatment of stumptail monkeys has demonstrated a variety of time related behavioral responses, a reduction in eating, but little change in sexual and dominance behaviors (28).

Interference with normal metabolic pathways also has been explored. Davis & Kohl (29) noted that the antiserotonergic drug methysergide facilitated lordotic responding in estrogen primed ovarectomized rats, and Everitt (30) has observed that the inhibition of serotonin uptake using chlorimipramine reduces proceptivity and receptivity in rhesus monkeys. Using 5-methoxy-*N, N*-dimethyltryptamine (a serotonin agonist) in selected members of group living stumptail monkeys, Schlemmer et al (31) found abnormal social and individual behavior patterns.

While far from complete, the preceding findings relating to Route *A* give a sampling of drug effects measured in social settings. Seemingly unrelated or contradictory findings may be explained in part by the effects of the different social and/or environmental conditions under which studies were conducted. These results underscore the necessity of specifying the research conditions under which studies are conducted.

Route B (Figure 1): Social Behavior—Pharmacological Relationships: Or, How Social Variables Influence the Effects of Pharmacological Agents

The effects of social status, if present, often have been uncontrolled sources of variance. However, a few investigators have examined these relationships, and findings with regard to social status strongly suggest that an animal's status may correlate with its behavioral response to selected pharmacological agents. Delgado et al (32), for example, have shown that in rhesus monkeys the effects of diazepam vary with an animal's position in the social hierarchy. Subordinant animals show larger changes in sleeping, alerting, locomoting, and grooming than dominant animals. Similarly, Sas-

senrath & Chapman (33) reported that in rhesus macaques delta-9-tetrahydrocannabinol has more of an effect on aggressive behavior in dominant animals than in subordinate ones. In studying the effects of amphetamine on rhesus monkey behavior, Haber et al (34) found that behavioral responses varied as a function of the animal's social status. In other studies, Sbordone & Garcia (35) have shown that untreated rats develop pathological aggression when paired with mescaline-treated rats in shock-elicited aggression conditions but not when paired with other untreated rats. Stern & Hartman (36) have reported reduced amphetamine lethality in rats following chronic social stress.

Behavioral response differences to drugs across status are not necessarily uniformly present and, if present, might not be significant. Thus, for example, parachlorophenylalanine appears to have highly similar direct effects on males of different social status (see below). That certain drugs have status-related effects while others do not is not surprising, but this fact does underscore the aforementioned point that we lack a theory of social behavior which is easily translated into physiological and biochemical terms.

Route C (Figure 1): Social Behavior and Environmental Variable—Biochemical-Physiological Relationships: Or, How Social and Environmental Variables Effect Biochemical and Physiological States

Considerable data are available concerning Route *C.* Studies of nonhuman primates have focused on relationships between social behavior and/or social status and a variety of peripheral biochemical parameters including, but not limited to, plasma cortisol (37, 38), plasma dopamine-beta-hydroxylase (39); plasma and platelet monoamine oxidase (40), plasma testosterone (41, 42), CSF 5-hydroxyindoleacetic acid (43), plasma free and bound tryptophan (44), and whole blood serotonin (45). In most instances relationships between behavioral or social variables and tissue variables have been found.

Several investigators have examined the association between basal and challenged plasma cortisol and social status. It is worthwhile discussing these findings in detail because they illustrate the problems of developing cross-species generalizations, the influence of research conditions on dependent variables, and difficulties involved in selecting dependent variables. Manogue et al (46) found that in squirrel monkeys high social status was associated with low basal plasma cortisol levels. These investigators used the direction of penile displays and success in overt aggressive behavior as criteria for assessing dominance. In apparent contrast to these findings, Mendoza et al (47) reported that when individually housed male squirrel monkeys were assembled into all male social groups, cortisol levels in-

creased in both low and high ranking animals. In no group did the dominant male, recognized by the directionality of hand grabs, have the lowest cortisol level. Moreover, this lack of relationship between dominance and low basal cortisol persisted when females were added to the groups and the groups were allowed to stabilize. Coe et al (38) also were unable to confirm a high status, low cortisol relationship in squirrel monkeys. In studies of established groups of squirrel monkeys, Manogue et al (46) have shown that dominant animals exhibited the greatest adrenalcorticoid reactivity as measured by plasma cortisol in response to physiologic (exposure to ether) and psychologic (exposure to a live snake) stressors. In apparent partial contrast to these data, Sassenrath (48) observed that in crowded groups of rhesus macaques, low-ranking animals exhibited the largest responses (assessed by urinary 17-OHCS) to an ACTH challenge. Elevated responses among subordinate animals were lowered by reducing "social stress," for example, by removing the dominant male within a group. Commensurate with Sassenrath's observations was Chamove & Bowman's (49) demonstration that in a small group of rhesus monkeys stress-induced increases in plasma corticoids were highest when an animal occupied a subordinate social position. At possible variance with these data, however, was the finding of Smotherman et al (50), that in rhesus monkeys infants of dominant mothers exhibited greater rises in cortisol following mother-infant separation than did infants of lower ranking mothers (see also 51).

A variety of other Route *C* findings have been reported. For example, Bowman et al (52) observed that in talapoin monkeys subordinate females do not have the luteinizing hormone surge which is normally induced by giving estrogen to female monkeys. Removal of rats from their cages results in an increase in plasma unesterified fatty acids and tryptophan concentrations in remaining animals (53). These findings are similar to those reported by Welch & Welch (54), who noted that the basal rate of formation of 5-hydroxyindoleacetic acid from whole brain serotonin is faster in grouped than in single mice. Henry et al (55) have found biochemical differences among rats at different times in group formation, and Laties & Weiss (56), in testing the effects of amphetamine, scopolamine, and pentobarbital on behaviors controlled by internal and external stimuli, found that behaviors controlled by internal stimuli are more resistant to drug-induced changes. Sulzman et al (57) tested for effects of various environmental variables on circadian timing systems in squirrel monkeys. Only light-dark and cycles of food availability were shown to be entraining agents in that they were effective in determining the period and phase of the rhythmic cycles.

In our view, these examples of Route *C* relationships serve as a reminder that it is essential to include a detailed analysis of social-environment variables in any study designed to assess the effects of drugs on behavior. This

point also may apply to selected drugs not normally considered to be affected by environmental or social variables (e.g. insulin).

Route D (Figure 1): Biochemical-Behavioral Relationships: Or, How Different Biochemical States Effect Behaviors

Route *D* has two main components. As indicated above, this route is part of the presumed sequence in nature of Route *A* (drug-behavior) relationships. In addition, whatever effects different biochemical states attendant with status may have upon behavior, whether primary or secondary, is organized here. We know both a great deal and very little about these relationships. A mass of empirical data has accrued describing drug effects upon neurobiological events, but much less data pertain to the neurobiological effects of physiological or biochemical parameters associated with status. The difficulty in either case is that no translation from neural events to behavior exists. Behavior is the integrated output of a number of interactive systems, and neural activities that make up these systems are likely to be discrete in time and localized in geography. Moreover, for many neurotransmitters it is not clear whether they "drive" a behavior or set the "neural tone" which permits a behavior to be driven by other systems (or both). Further interpretative difficulties can be envisioned. For example, balance among neurotransmitter systems, as well as sensitivity of postsynaptic neurotransmitter receptors, may differ as a function of an animal's age, sex, previous experience, and/or social status. Or, because of threshold effects, transmitter changes of equivalent absolute amounts may result in minimal behavioral changes in one animal but obvious changes in another.

Perhaps the most important point to stress is that studies of Route *D* relationships will remain incomplete until the reciprocal effects of social and environmental variables on biochemical and physiological states (Route *C*) are taken into account.

Route E (Figure 1): Pharmacological—Biochemistry-Physiology Relationships: Or, How Pharmacological Agents Alter Biochemical and Physiological States

By far most of the studies relevant to Route *E* derive from investigations of nonprimate species. For example, rats treated with *p*-chloroamphetamine show acute hypophagia, hypodipsia, and body weight loss (58). Progressive cocaine treatment in rhesus monkeys leads to an increase in homovanillic acid in the cisternal cerebrospinal fluid (25). Barber et al (59), treating sheep with L-tryptophan, have noted both general increases in CNS tryptophan and differential increases in different brain areas; similar findings were observed for brain serotonin and 5-hydroxyindolacetic acid.

Generally, pharmacological alterations of metabolic processes that are common to all tissues will induce analogous changes in those tissues. For example, administration of the serotonin precursor tryptophan to rats increases brain, blood, and gut serotonin, whereas inhibition of the enzyme tryptophan hydroxylase (essential to serotonin biosynthesis) by parachlorophenylalanine reduces serotonin levels at the same sites (60, 61). On the other hand, chlorgyline inhibits both platelet and brain monoamine oxidase A, but the brain, and not platelets, also contains monoamine oxidase B which is less affected by chlorgyline (62). Thus, for another group of agents there are likely to be both similarities and differences between tissues in their responses to pharmacological agents. Further, species may differ in the subtleties of metabolic control so that findings in one species, while frequently generalizing to other species, may not be totally correspondent. Many of these points are illustrated in the human literature on the effects of MAO inhibitors (see 63) in which some of the varying effects of related drugs may be explained by such phenomena as differential tissue effects, carrying capacity across the blood-brain barrier, and induced compensatory mechanisms.

Route F (Figure 1): Biochemical-Pharmacological Relationships: Or, How Different Biochemical-Physiological States Effect Pharmacological Agents

Route *F* is the route for which there is the least empirical data concerning mechanisms and functions. Currently, considerable interest has been shown in both basal and response levels of cortisol as a method of predicting responses to selected drugs, but findings are still inconclusive. In our view, the initial steps in examining relationship associated with this route are to study the effects of selected biochemical parameters on the metabolism of pharmacological agents already known to alter behavior. For example, through studying the behavioral and physiological changes in rhesus monkeys produced by exogenous ACTH, Sassenrath (48) has shown that chronic low status may be associated with elevated adrenal corticoid production. In studies of rats (under selected conditions) both corticoids and tryptophan have been shown to induce tryptophan oxygenase (64, 65). If low status animals have elevated corticoid levels, they may also possess higher tryptophan oxygenase levels, which may result in more tryptophan being catabolized into kynurenine and less being available for entering the brain. In turn, this may result in altered central serotonin biosynthesis, which may in part contribute to the difference in behavioral effects. Treatment of low status animals with tryptophan would thus be expected to produce responses different from those found in comparably treated high status animals.

We have briefly reviewed selected findings and research issues relevant to sociopharmacology. While there is evidence supporting each of the postulated routes in Figure 1, interrelationships between the routes are still far from clear.

A BRIEF REVIEW OF THE AUTHORS' STUDIES IN SOCIOPHARMACOLOGY

In most instances, the data reviewed below have been reported elsewhere in greater detail (44, 45, 66–68). The studies reported below are limited to vervet (*Cercopithecus aethiops*) monkeys.

Route A (Pharmacological-Social Behavior Relationships)

Vervets given once daily doses of tryptophan (20 mg/kg, i.p.) over a two week period show an increase in behaviors associated with socialization and a decrease in behaviors regarded as accompanying fear or anxiety (66). Both dominant and nondominant animals increased the frequency of the behaviors approach, groom, rest, and eat and decreased the frequency of locomotion, being solitary, being vigilant, and avoiding. Following the cessation of treatment, all animals returned to base line frequencies of these behaviors. In contrast, when 20 mg/kg of tryptophan has been given for 20 consecutive days to dominant animals we have not detected a shift in social status; this finding suggests that the kinds of tryptophan-induced behavioral differences observed above do not alter dominance relationships.

Another set of studies has shown that the behaviors of untreated animals within the same social group may be affected by changes in individual animals receiving drug treatment. Among male animals, chronic treatment with parachlorophenylalanine (80 mg/kg/day for 14 days) resulted in irritable, aggressive, and hypermobile behavior (66). Animals of different social status showed similar behavior responses to this drug. When the dominant male only was treated, the frequency of grooming among nontreated, nondominant group members dramatically and significantly decreased. In contrast, when a single nondominant group member was similarly treated, no change in the grooming behavior of other, nontreated animals was observed. (This example also would apply to Route *C*.)

Route B (Social Behavior-Pharmacological Relationships)

As noted above (first study, Route *A*) in mixed-sex captive vervet groups, behaviors of adult males change in response to chronic tryptophan loading. For dominant males, however, changes in the behaviors approach, groom, eat, and rest were significantly greater than for nondominant males (66).

In a related set of studies we have continually monitored the behavioral effects of acute tryptophan (20 mg/kg) from 0 to 180 minutes post administration. During the first hour, dominant males, when compared to nondominant males, exhibited significantly larger increases in the behaviors resting and eating, and larger decreases in being vigilant and being solitary. This differential responsivity persisted through the second and third hours post-tryptophan administration (M. J. Raleigh, G. L. Brammer, and M. T. McGuire, unpublished data).

Route C (Social Behavior-Biochemical Relationships)

We also have examined aspects of the relationship between whole blood serotonin and social status in vervet monkeys. In captive vervet groups, whole blood serotonin levels are significantly higher in dominant males than in other males [Mean $\pm$ SEM (N); dominant vs nondominant; 937 $\pm$ 31 ng/ml (17) vs 650 $\pm$ 23 ng/ml (39); $df = 38$, $t = 7.14$, $p < 0.001$]. In addition, in each of the 17 groups studied thus far, the dominant male had the highest serotonin level (66). In drug-free vervets living in stable social groups, intraindividual variation in whole blood serotonin is low (Pearson product-moment correlations $r < 0.95$ for repeated measures), and there are no significant seasonal or circadian fluctuations in whole blood serotonin concentrations (M. J. Raleigh, G. L. Brammer, and M. T. McGuire, unpublished data). It is unlikely that the observed differences in whole blood serotonin arise from dietary differences or from differential response to capture, restraint, or blood collection.

In studies in which social status has been behaviorally manipulated, changes in whole blood serotonin similar to those noted above have occurred in both dominant and nondominant males: nondominant males who become dominant change from the 500+ ng/ml range to the 900+ ng/ml range; conversely, dominant males who decline in status show the reverse changes. Dominant males who have become nondominant spontaneously have exhibited a decline in whole blood serotonin from the 900 ng/ml range to the 500 ng/ml range, whereas nondominant animals who have became dominant show the reverse changes (M. J. Raleigh and co-workers, unpublished data).

A related finding is as follows: dominant animals who are isolated from their group or who are housed with adult females only, show a rapid decline in whole blood serotonin (900+ ng/ml to 500+ ng/ml) over an 8–10 day period (M. J. Raleigh and M. T. McGuire, unpublished data). These findings strongly suggest that the differences in whole blood serotonin result from adult male-adult male interactions.

Other pilot data show platelet differences correlated with social status differences. In the two groups examined to date, the dominant male ani-

mals, who had whole blood serotonin levels about 40% greater than nondominant animals, had only about half the number of circulating platelets as seen in nondominant animals (G. L. Brammer, M. J. Raleigh, A. Yuwiler, and M. T. McGuire, unpublished data). This finding was observed consistently on repeated sampling days, was stable over a brief time series, was independent of variations in the platelet harvesting procedure, and was not an artifact of different platelet size distributions. The startling consequence of this result is that when expressed as serotonin concentration per platelet, the difference between dominant and nondominant animals is threefold.

Preliminary findings relating to basal cortisol levels suggest differences in serum cortisol levels as a function of social status. Thus far, high status animals ($N = 6$) have had high basal cortisol levels (5 of 6 cases) whereas low status ($N = 10$) animals have low levels (8 of 10 cases) (G. L. Brammer, M. T. McGuire, and M. J. Raleigh, unpublished data).

Route D (Biochemical-Behavioral Relationships)

We have used a battery-of-drugs strategy to examine serotonergic contributions to behaviors (44). Because any pharmacological agent may affect several transmitter systems, and because any behavior is likely to be affected by many transmitter systems, we have attempted to parcel out relative (rather than absolute) serotonergic contributions to behaviors. We applied this strategy by treating group living adult vervet monkeys with chronic tryptophan, parachlorophenylalanine, 5-hydroxytryptophan, the monoamine oxidase inhibitor chlorgyline, and parachlorophenylalanine followed by 5-hydroxytryptophan. The effects of these treatments on a variety of behaviors were monitored. We assumed that tryptophan, the natural precursor to serotonin, and parachlorophenylalanine, an inhibitor of tryptophan hydroxylase, were fairly specific for serotonergic systems, although both drugs may also affect other systems as well. Parachlorophenylalanine, while producing a long-lasting effect on tryptophan hydroxylase, also causes a transient reduction in tyrosine hydroxylase. 5-Hydroxytryptophan, which is intermediate between tryptophan and serotonin, was assumed to have less specificity for serotonergic neurons because it can also enter catecholaminergic neurons and be decarboxylated, and the resultant serotonin can act as a false transmitter. Chlorgyline was thought to have little specificity for the serotonergic systems, since monoamine oxidase is common to both serotonergic and catecholaminergic neurons and is involved in the metabolism of both. In terms of the polarity of alterations in neurotransmission efficiency, tryptophan, 5-hydroxytryptophan, and chlorgyline should enhance, and parachlorophenylalanine treatment decrease, serotonergic effects. It was expected that the administration of 5-hydroxytrypto-

phan subsequent to parachlorophenylalanine would reverse, at least in part, the parachlorophenylalanine effects on serotonergic systems.

Based on these criteria, serotonergic systems would be implicated in the mediation of a behavior if tryptophan and parachlorophenylalanine produced opposite effects. Serotonin was viewed as a strong mediator if, in addition, 5-hydroxytryptophan and chlorgyline treatments resulted in tryptophan-like behavioral effects, and 5-hydroxytryptophan reversed at least part of the behavioral effects of parachlorophenylalanine. However, chlorgyline treatment elevates both serotonin and norepinephrine (and, to a lesser degree, dopamine). Consequently, for behaviors which are largely dependent on norepinephrine and for which norepinephrine effects are weakly antagonized by serotonin, chlorgyline should produce behavioral changes different from those resulting from tryptophan. Chlorgyline should be without effect if norepinephrine and serotonin are equally balanced and antagonistic in the mediation of behavior. Finally, if norepinephrine contributes little to the mediation of a behavior or if norepinephrine and serotonin interact synergistically in the mediation of behavior, then chlorgyline should produce tryptophan-like effects. Results from a number of studies have largely supported this reasoning. Findings are summarized in Figure 2.

Route E (Pharmacological-Biochemical Relationships)

In another set of studies, we have preliminarily examined whole blood serotonin at 0, 40, 60, and 80 min post tryptophan administration (20 mg/kg L-tryptophan i.p.) in four nondominant and two dominant males. Dominant males exhibited larger absolute and relative (as percent of baseline) increases in whole blood serotonin at 40, 60, and 80 min (M. J. Raleigh, G. L. Brammer, and M. T. McGuire, unpublished data).

	TREATMENT				
	TYRPT	PCPA	5-HTP	CHLORG	PCPA-5HTP
BEHAVIOR	BEHAVIORAL EFFECTS				
GROOMING	△	▽	△	△	△
APPROACH	△	▽	○	△	△
REST	△	▽	○	○	○
EAT	△	▽	○	○	○
LOCOMOTION	▲	▼	○	○	○
SOLITARY	▲	▼	○	▲	▼
AVOID	▲	▼	○	▲	▼
VIGILANCE	▲	▼	▼	▼	○
AGGRESSION	○	▼	▼	○	▽
HUDDLE	○	▽	○	○	○
SEX	○	○	○	○	○

Figure 2 Summary of the behavioral effects using a battery-of-drugs strategy to examine serotonergic contributions to behaviors. An increase in a behavior is illustrated by an upright triangle. The inverted triangle represents a decrease in a behavior. No change is represented by a circle.

Route F (Biochemical-Pharmacological Relationships)

The finding of a heightened whole blood serotonin response in dominant animals to a tryptophan load, when combined with the previous findings that dominant males who are either isolated or housed with adult females only have whole blood serotonin levels comparable to nondominant males, suggests the following point: the effects of a pharmacological agent (e.g. tryptophan) will be altered as a function of the physiological state of an animal, itself a function of social variables.

GENERAL RESEARCH IMPLICATIONS, RESEARCH PROBLEMS, AND PITFALLS

A number of review articles are available which consider different facets of sociopharmacology. Sassenrath & Chapman (33) have discussed primate social behavior test systems to characterize alteration of CNS function by telestimulation and psychoactive drugs. Kalverboer (69) has reviewed the use of direct systematic observation in human psychopharmacology studies and van Hooff (70) has reviewed behavioral pharmacology. Research designs for studying drug-environment-behavior relationships have been discussed and developed by Liberman et al (71) and Kohnen & Lienert (72) have evaluated possible research paradigms. Hammond & Joyce (73) have edited a volume containing a variety of studies dealing with the effects of psychotropic medications on behaviors related to socialization.

Whereas sociopharmacology has numerous methodological and interpretative obstacles, the potential value of research in clinically related areas outweighs the obstacles. Undoubtedly the most important question which might be answered would relate drug effects to social consequences resulting from drug-induced behavioral changes. A related question concerns medication choice, which might be considerably improved with a clarification of the routes associated with the model. To answer these questions, however, many, if not all, related routes must be investigated.

What are the problems inherent to sociopharmacology? A number of these already have been discussed or strongly implied. Others will be briefly mentioned here. A major problem concerns tissue availability. In most sociopharmacological studies one tries to keep test animals alive. Thus, it is often necessary to work with peripheral rather than CNS tissues. To do so raises a whole new set of questions concerning the relevance of peripheral findings to CNS mechanisms and functions. Many drugs, for example, do not cross the blood brain barrier. Others are significantly altered before they do. Thus, there are definite limitations concerning the specificity with which CNS-related questions can be answered unless other techniques are used. A second problem is that few, if any, pharmacological agents are specific for a single biological or neurotransmitter system. When this fact is added

to findings which demonstrate (*a*) that drugs have different behavioral effects at different doses, (*b*) that there are species differences in response to drugs, and (*c*) that animals may be physiologically different as a function of social or physical environmental variables, then it is clear that studies often require a large number of groups and closely controlled conditions (or studies under multiple conditions) before data will be compelling.

Another major problem concerns social behavior itself. Most studies simply record behavioral frequency changes in response to drug effects. However, in most instances we have no idea of how important these changes are and what long range adaptation and/or physiological effects they may have. Although findings amply demonstrate social status effects on biochemical parameters and response to pharmacological agents, social status is but one of many variables relevant to the day-to-day life of social groups. Moreover, social systems change, even under the most stable of conditions, and different dominant male and female animals have different "personalities." Thus, not only the characteristics of social systems but many other characteristics as well (e.g. personalities, kin relationships, physical environmental variables, previous experiences, etc.) may have to be taken into consideration to assess drug effects.

Other problems also can be identified. For example, Elias et al (74) found that mice genetically selected for blood pressure extremes differed in their aggressive behavior: high blood pressure mice were less aggressive socially than low blood pressure mice. Thus, consideration of genetic characteristics in otherwise normal animals may be essential in evaluating drug responses. Sex differences also may influence pharmacological effects. For example, in comparing isolated with group living golden hamsters, Brain (75) has observed that changes in adrenal weight differ across sexes—males have a greater increase.

CONCLUSION

We have presented a review of sociopharmacology from our perspective. In a field so broad and in many ways still searching for self-definition, we realize that any two reviews would be vastly different. Throughout this review, two points have impressed us. First, studies in sociopharmacology are very much in need of attending to the wide number of possible outcome-influencing variables. Second, more than one route in Figure 1 should be studied by individual investigators so that a more coherent picture of reciprocal effects begins to emerge. While we have searched for treatment implications throughout our review, we believe it would be premature to suggest them. Yet clearly implications exist. For example, it may be necessary to develop different pharmacological agents for persons of different social status or living in different environments.

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