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Drug Discrimination in Neurobiology

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COLPAERT, F. C. *Drug discrimination in neurology.* PHARMACOL BIOCHEM BEHAV. **64**(2) 337–345, 1999.—Areas of neurobiological interest are identified towards which drug discrimination (DD) studies have made important contributions. DD allows ligand actions to be analyzed at the whole organism level, with a neurobiological specificity that is exquisite and often unrivalled. DD analyses have thus been made of a vast array of CNS agents acting on receptors, enzymes, or ion channels, including most drugs of abuse. DD uniquely offers access to the study of subjective drug effects in animals, using a methodology that also is transposable to humans and has generated unprecedented models of pathology (e.g., chronic pain, opiate addiction). Parametric studies of such independent variables as training dose and reinforcement provide refined insights into the dynamic psychophysiological mechanisms of both drug effects and behavior. Three different mechanisms have been identified by which discriminative, and perhaps other behaviors, can come about. DD also is superbly sensitive to small, partial activation of molecular substrates; this has enabled DD analyses to pioneer the unravelling of molecular mechanisms of drug action (attributing, f.ex., LSD's particular subjective effects to an unusual, partial activation of 5-HT, and perhaps other receptors). DD has both oriented and served as a tool to conduct drug discovery research (e.g., pirenperone-risperidone, loperamide). The DD response arguably constitutes a quantal, rather than graded, variable, and as such allows a comprehension of molecular, pharmacological, and behavioral mechanisms that would have been otherwise inaccessible. Perhaps most important are the following further contributions. One is the notion that particular, different levels of receptor activation are associated with qualities of neurobiological actions that also differ and are unique, this notion arguably constituting the most significant addition to affinity and intrinsic activity since the earliest theoretical conceptions of molecular pharmacology. Another contribution consists of studies that render redundant the notion of tolerance and identify fundamental mechanisms of signal transduction; these mechanisms account for apparent tolerance, dependence, addiction, and sensitization, and appear to operate ubiquitously in a bewildering array of biological systems. © 1999 Elsevier Science Inc.

Drug discrimination Neurobiology Review

DRUG discrimination (DD) is a paradigm of behavioral pharmacology that was developed in the 1970s, partly as an effort to remedy what were perceived to be the limitations of the State Dependence paradigm. Indeed, studies of drug states that employed this latter paradigm found such states to be produced only at very high, often toxic drug doses, suggesting the states to be of little relevance to the agents' neurobiological actions (120,123). The State Dependency protocols then used also generated data that were poorly reproducible (67,119,153) and of a complexity that often defied interpretation (121,149). Although it appears (19,27,59) that the two paradigms fundamentally address different phenomena, studies of State Dependence have largely been abandoned since the 1970s, while DD research in the meantime became widespread. Indeed, and perhaps owing to the availability of DD protocols (19) that reliably and efficiently generated intelligible data on low doses of CNS agents, DD research gained a momentum that sparked the organization, now 20 years ago, of the first (36) of a series of international meetings, and left in its wake the creation of two scientific societies, the SSPD and the EBPS (146).

In this article, we will identify the areas of neurobiological science in which, in the author's view, DD research has made important, at times unique, contributions. Limitations of the present overview are that it reflects the author's perception and does not attempt to present an exhaustive and systematic analysis of the 2576 publications that are comprised in the December 1997 version of the DD Bibliography (148). In particular, many of the conceptual innovations that have been accomplished by DD research utilized opiate receptor ligands; we will focus here on such seminal studies.

THE DD PARADIGM

In a typical DD experiment, animals are trained to discriminate the injection of a particular dose (the training dose) of a particular drug (the training drug; D) from the injection of saline (S). For example (19), food-deprived rats can be trained to press one of two levers for food in daily 15-min sessions; arrangements are made so that, at some time before the sessions, the animals are injected with either D or S. After D injection, the animal is required to press one lever (the drug lever, DL) to obtain food, and presses on the other lever do not yield food. After S injection, the animal now is required to press the other, saline, lever (SL) and presses on the DL then are inconsequential. Training is implemented until the animal reliably selects the appropriate lever after injections of either D or S. Once trained, the animals can be used to con-

duct tests of stimulus generalization. To this end, the animal is administered, before the test session, a test treatment that can be either saline, the training dose, any other dose of the training drug, or indeed any dose of any other agent. In the test session, it is determined which of the two levers, DL or SL, the animal selects. If the test treatment makes the animal select the DL, then it is considered that stimulus generalization occurred between it and D; it is inferred that the test treatment produced a discriminative stimulus that is qualitatively similar to that produced by D. If the test treatment makes the animal select the SL, then it is considered that it did not produce a stimulus similar to that produced by D (i.e., that it did not produce stimulus generalization). Tests that are thus conducted with lower-than-training doses of the training drug typically show the generalization to vary in an orderly fashion with the test dose; it does not occur with very small doses, and progressively increases as the test dose is larger. The function relating the test doses to the thus growing amplitude of generalization is called a stimulus generalization gradient. The protocol outlined here is one that has been implemented very widely, although many procedural variants are possible (53).

NEUROBIOLOGICAL SPECIFICITY

Early DD studies utilizing opiate training drugs revealed the paradigm to demonstrate exquisite molecular specificity. Thus, rats trained to discriminate fentanyl or morphine from saline showed orderly dose-dependent generalization with lower doses of the training drug and with other compounds that were known to act as agonists at opiate receptors (13,14,140). This generalization was antagonized by naloxone and other putative opiate antagonists. The generalization also displayed the stereoselectivity that opiate receptor ligands were know to possess, and very importantly, did not occur with any of a vast array of CNS and other agents that do not act on opiate receptors (28,81,87). The potency with which generalization occurred covaried highly, if not perfectly, with that with which opiates produce their arguably most characteristic and most extensively studied in vivo action, i.e., analgesia (21). Yet, this analgesic action does not subserve the opiates' discriminative effects; indeed, apparent tolerance to analgesia may develop in animals in which opiate DD remains unaltered (17,29), and nonopiate analgesics do not generalize to opiate training drugs (22). Also, and inasmuch as there are multiple opiate receptors, patterns of generalization faithfully reflect the type or types of opiate receptors at which act both the training drug and the ligands being tested (81,88).

Thus, opiate DD appears to fully and exclusively reflect at the, in vivo (i.e., highly integrated, behavioral) level of analysis, the molecular association (i.e., binding) that occurs between a given [exogenous, or for that matter, endogenous; (150)] agent and its biological substrate. The exquisite specificity that the DD paradigm thus offers with opiates is also found with other, nonopiate, CNS agents (see below), and is often unrivalled by other methods of in vivo analysis, be they behavioral or otherwise. Note that this specificity is not invariably molecular in that it may not always relate to one particular molecular site of initial drug action. For example, the specific DS effects shared by the CNS agents may involve a common activation of postsynaptic dopamine receptors, but this activation may variously result from upstream effects on neurotransmitter reuptake, release, and degradation (30,33,39). The specificity of the DD paradigm, thus, is one that can occur at molecular and cellular levels, and can perhaps best be referred to as neurobiological.

AN IN VIVO TECHNIQUE OF NEUROPHARMACOLOGY

The specificity and the further features, discussed below, of the DD paradigm, have made of DD a now widely used technique of behavioral pharmacology, assaying at a whole organism level of analysis various ligands that act at such molecular substrates as ion channels, enzymes and, in particular, the seemingly unlimited diversity of neurotransmitter receptor types and subtypes. Among the ligands that have been studied as such are the CNS stimulants cocaine and amphetamine (39,84), inhibitors of monoamine oxydase (42), and of monoamine uptake (166), benzodiazepines (16), barbiturates (157), and ethanol (7,94), cannabinoids (93), hallucinogens (74,105,158), phencyclidine and ketamine (82,86,125), physostigmine (96), caffeine (90), nicotine (133,144), pentylenetetrazole (141), melatonin (106), and different volatile agents (4,68,129,130). If in this manner DD has been employed to examine medically relevant agents, the paradigm has similarly been utilized to study ligands at receptor systems for dopamine (15,85,99,162), serotonin (40,78,156), acethylcholine (97, 98,134), noradrenaline (9,50,118,135), GABA (16,157), and also histamine (122,159), NMDA (2), adenosine (12,143), CCK (112), and insulin (136). Finally, while some receptor ligands may not readily be amenable to direct DD analysis (i.e., cannot readily be implemented as training drugs), indirect methodologies do permit their actions to be analyzed in the DD paradigm. For example, DA receptor antagonists effectively interfere with the discrimination of DA agonists and CNS stimulants (18,30,33,115), and opiate antagonists become readily discriminable in opiate-dependent subjects (89). It thus appears that the DD paradigm allows one to address an extremely wide, seemingly unlimited, array of molecular substrates that are of neurobiological interest.

The particular research areas of neuropharmacological interest that are accessible to DD analysis are numerous and diverse. Thus, the DD paradigm has successfully been employed to study kinetic, temporal features of drug action (8,29,80,128), reversibility of ligand–receptor binding (69), stereospecificity (75,117,155), and structure–activity relationships (61,76,79,163), agonist–antagonist interactions (70), and pA_2 characteristics (10,151), receptor supersensitivity (5,6), central vs. peripheral sites of drug action (14,21,71), and also, neurotoxicological effects of therapeutic agents (132).

SUBJECTIVE EFFECTS AND DRUG ABUSE

Although in the previous section we have found DD to be a particularly valuable technique of neuropharmacological research, the drug-produced discriminative stimulus, in the first instance, constitutes a special physiological phenomenon. The definitive identification of this phenomenon will likely require many more years of more sophisticated research, but early studies of opiates (13,14,24) have provided initial evidence that drug-produced discriminative effects ar homologous to the characteristic subjective effects that these agents produce in humans (1,127,137). Thus, while at some point in time it was felt that subjective experiences were uniquely human and utterly inaccessible, DD carries the exciting promise of rendering amenable to experimental analysis in animals experiences, which, by their nature, have been considered as out of the range of scientific inquiry.

Many so-called drugs of abuse (i.e., of nonmedical, allegedly recreational, and often illicit use) are noteworthy for the subjective effects (e.g., euphoria, relaxation, hallucinations) that they produce. DD studies of such abused agents as opiates, CNS stimulants, cannabinoids, and ethanol (62,95) have

found discriminative effects to indeed be homologous to the subjective effects that these agents produce in humans, and the DD paradigm is now also being implemented with human subjects (11).

The access which DD offers to the experimental analysis of subjective experiences has naturally made it possible to examine the neurobiological mechanisms of such experiences. Research is currently ongoing to investigate these mechanisms in terms of their molecular (152,161), neuronal (91), and neuroanatomical substrates (65,116,160).

Another, practical spinoff has been the deployment of the DD paradigm in the preclinical evaluation of drug abuse potential. The paradigm has been used to this effect with opiates (13,14,25) and a host of other, often newly synthesized, agents (4,77,126,138,139,145).

MODELLING PATHOLOGY

As indicated above, the DD paradigm makes subjective drug effects accessible for empirical, experimental research. This unique feature also confers on the DD paradigm an equally unique capability to model certain pathologies in terms of the subjective experience with which they are associated.

Of all human pathology, pain arguably represents the one instance where the suffering is most comprehensively defined by subjective perception. Indeed, pain in essence is a subjective experience (113), and even today's technically sophisticated research utilizes nothing other than surrogate parameters to study pain in all cases except, of course, that of conscious humans. It was because of the inaccessibility of the subjective pain experience in animals that early this century Sherrington (142) proposed and defined the so-called pseudoaffective response as a surrogate measure of at least acute pain in animals [see (54)]. This pseudoaffective response comprises such now widely used elements as tail flicks, paw licking, and abdominal writhing in rodents. One consequence of the common albeit often implicit acceptance of Sherrington's proposal has been that, until today, virtually all research on acute pain concerns pseudo or surrogate responses, but not pain itself. Another consequence has been that chronic pain has been left largely unexplored; Sherrington's proposal concerned acute pains only, and did not address the question as to how chronic pain in animals should possibly be measured, if indeed it exists at all. It is only in much more recent times that true de novo and painstaking research efforts have allowed the identification and substantial validation of the rat with adjuvant arthritis as an instance and model of chronic pain in animals (54). It has been the availability, then, of this animal model of chronic pain and of the DD paradigm as a model of subjective experience, that has made possible a true feat; arguably for the first time ever has been made an actual observation of chronic pain in animals. That is, Weissman (154) demonstrated that unlike normal control animals, rats with adjuvant arthritis can discriminate the analgesic aspirin from vehicle, this discrimination arguably being based on the presence (in vehicle sessions) or relative absence (in aspirin sessions) of subjectively experienced pain. Although this finding remains to be replicated and much further work is in order, the observation did at least in principle and at an early stage exemplify in what manner the DD paradigm can uniquely offer access to the study of the paramount subjective experience that is chronic pain.

Another, highly innovative DD model of subjective pathology involved rats that were rendered opiate dependent by the chronic administration of morphine. Dependent rats were found to readily discriminate opiate antagonists (73), and pharmacological analysis (89) of stimulus generalization in these animals suggests that they specifically discriminate the subjective experience of opiate withdrawal. Inasmuch as this latter experience may constitute the hallmark feature of opiate addiction (60), the DD paradigm again offers a unique access to a pathology that remains largely unresolved and is chiefly characterized by a specific subjective experience [for review, see (72,108)].

PSYCHOPHYSIOLOGY OF SUBJECTIVE PERCEPTION

The DD paradigm thus appears to offer an experimental access to the subjective experience, or perception, of stimuli that are produced by drugs or that arise from other, physiologically defined, but invariably internal conditions (19,26). In this capacity, DD studies have begun to provide insights into the psychophysiology of subjective perception. Among the factors (53) that have been found to determine the subjective perception are training dose [for review, see (58)] and discriminability (41), the manipulation of reinforcement (43,63, 100,109), and the alternative stimulus from which a given drug stimulus is to be discriminated (44). It thus appears that the subjective perception that is induced by one particular agent such as fentanyl, can vary in orderly but astonishingly multiple and diverse ways. Also intriguing have been findings (32,35) that large, orderly oscillating changes in sensitivity (i.e., lowest generalized dose) occur by some rhythmic process that remains to be identified.

MECHANISMS OF BEHAVIOR

In the DD paradigm one typically manipulates, as an independent variable, some (training) drug acting on a particular molecular substrate (e.g., the opiate fentanyl); and one physically measures as the dependent variable, some behavior such as food-rewarded lever pressing (19). The DD paradigm thus also is a paradigm of behavioral pharmacology and in that capacity allows one to address the question as to how behaviors can come about. More specifically, the paradigm allows, at least in principle, that the entire range of mechanisms that enter into operation be examined, from the molecular site of drug impact to the pressing of a lever. Although those mechanisms likely are manifold, DD studies have revealed that at least three levels of analysis must be considered to account for the data (51), i.e., the molecular, the cell-physiological, and the behavioral level. DD studies, then, have so far identified three different sets of mechanisms by which the same lever press behavior (i.e., at least partial drug appropriate responding) can occur.

The first set of mechanisms is exemplified by other opiate agents as they produce DL responding in animals trained to discriminate an opiate from saline (28). This often-encountered set of mechanisms is one whereby the agent being tested binds to the same molecular substrate (e.g., neurotransmitter receptor) as the training drug, and there causes an action (i.e., activates or inhibits the substrate) that also is similar to that produced by the training drug. This similar receptor/cellular action in turn causes a stimulus generalization, which is expressed behaviorally as drug-appropriate responding. An early example of the second set of mechanisms concerned the effects of fentanyl in rats trained to discriminate apomorphine from saline (23). Here, the test agent binds to a different molecular substrate from the training drug, but causes a similar cellular action downstream of its substrate interaction (e.g., postynaptic dopamine receptor activation).

The latter again causes stimulus generalization. The third set of mechanisms is exemplified by the effects of NMDA antagonists in rats discriminating fentanyl from saline (102,103). Here, the test agent not only binds to a different molecular substrate but also causes dissimilar cellular actions. However, the test agent produces a mnemonic state in which the recall is hampered of the (drug) discrimination that was previously learned in another, often normal, state. Thus, failing to recall the discriminative control of lever-press responding, the drug-lever responding that does occur in these conditions results from state dependency, rather than stimulus generalization (92,102).

Of these three sets of mechanisms, the first has been studied in greatest detail, and offers a breathtaking view of the elegantly coherent mechanisms whereby behavior can come about throughout these three levels of analysis (51). It is useful to note that this account contends that the drug discriminative response is quantal rather than graded in nature (19,51,53,58). There exists no consensus on this latter issue (131,147,165), but no accounts have so far been offered, and perhaps cannot be given, that would equally coherently explain the available evidence at these three levels of analysis, while assuming the discriminative response to be graded.

THE THIRD DIMENSION OF MOLECULAR PHARMACOLOGY

Early studies (20) found the DD paradigm to be superbly sensitive to the effects of opiate receptor ligands possessing only weak or partial efficacy. Experimental (39,48,52) and theoretical analyses (51,55,101) of the partial generalization and of the other, complex, effects that partial receptor agonists produce in the DD paradigm have discovered an exceptionally interesting and important phenomenon. In essence, the phenomenon signifies that a particular magnitude of receptor activation is associated with a quality of discriminative effects that is unique to that particular magnitude, other magnitudes generating other, particular, qualities. Thus, there appears to exist a relationship between a quantitative (i.e., magnitude of receptor activation) and a qualitative variation (i.e., quality of discriminative effect) that is not unlike one encountered in vision. In vision, quantitatively differing wavelengths of optic energy are also associated with effects (i.e., colors) that differ qualitatively.

The potential ramifications of this discovery may be most considerable. Theory in molecular pharmacology devised, brilliantly for that matter, two abstract notions that allow us to comprehend the effects of pharmacological agents. One is that of the receptor, introduced by Ehrlich (83), as the molecular locus or substrate on which different agents can act and interact as a function of the affinity that they possess for the receptor. A second notion, introduced by Ariëns (3), is that of intrinsic activity, also termed efficacy; receptor ligands are endowed with an intrinsic ability to activate the receptor to an extent that can vary from zero to maximal activation [more recent developments also allowing for smaller-than-zero or inverse activation of the receptor; (114,124)]. Thus, current theory in molecular pharmacology eventually accounts for the effects of pharmacological agents by defining agents along the two dimensions of affinity and efficacy; any qualitative variation that occurs being ascribed to the operation of additional receptors. The DD finding appears to make this account no longer sufficient, and two possibilities arise (51) to incorporate the new finding. One is to add a third dimension, allowing quantitatively different levels of activation of the same receptor to yield responses that differ qualitatively but belong to a single response family. A second possibility is to introduce the concept that different levels of receptor activation cause the receptor to assume configurations in which it is coupled to different effectors yielding qualitatively different responses. In this second possibility, the receptor in effect is not the same, but instead represents by itself a family of receptors that can comprise numerous members.

Another, related, ramification of this DD finding is that the psychopharmacological actions that CNS agents produce, can differ and may, in a qualitative manner, vary as a function of this intrinsic activity. We have chosen to analyze this latter issue with agonists at 5-HT_{1A} receptors. A first extensive analysis of available and newly synthesized 5-HT_{1A} ligands found the magnitude of the anxiolytic-like activity of the ligands to be a function of the ligands' differing, intrinsic activities (57). Further studies of both anxiolytic- and antidepressant-like activities found (64,104) that the magnitude of intrinsic activity required to produce antidepressant-like effects is larger than that required to produce anxiolytic-like effects. The available evidence, thus, is consistent with the notion that qualitatively differing anxiolytic-like and antidepressant-like effects are generated by different-magnitude activations of 5-HT_{1A} receptors. Conversely, and no less excitingly, this evidence may also suggest that anxiety and depression are qualitatively differing pathologies that belong to the same family and differ in terms of the level of 5-HT_{1A} receptor activation with which they are associated.

MOLECULAR AND CELLULAR MECHANISMS OF DRUG ACTION

The notion, derived from studies of opiates, that a particular magnitude of receptor activation may generate a particular, unique, quality of subjective experience, has made us analyze LSD's molecular actions in this light. It appeared (40,45) that agents then known as 5-HT antagonists, partially antagonized LSD's DS effects, but also produced partial generalization, the sum of these partial antagonist and agonist effects amounting to about 100%. A parsimonious account of these findings is that in producing its DS effects, LSD acts as a partial agonist at 5-HT receptors, generating a magnitude of receptor activation that is weak enough for it to be partly mimicked by at least some concentrations of other, even more weakly efficacious, 5-HT receptor ligands. At the same time, the LSD-induced activation is large enough for other concentrations of these even more weakly efficacious ligands in other animals to antagonize it. Thus, the particular subjective effects (e.g., hallucinations) that LSD produces may arise from the particular partial activation that LSD produces of 5-HT receptors (51). Agents that activate these receptors to an either lesser or greater extent, should not produce the same quality of subjective effects (e.g., not be hallucinogenic). This account explains the relative uniqueness of LSD's hallucinogenic potential, and is compatible with more recent data (66,107) on LSD's cellular actions.

The case of LSD thus exemplifies how the DD paradigm is capable of specifying not only the molecular site(s) of drug action, but also the equally intricate, downstream cellular mechanisms that may account for LSD's unique actions, and that for so long have remained elusive.

DRUG DISCOVERY

Because the DD paradigm enables one to unravel molecular, cellular, and psychophysiological mechanisms of drug action, it comes as no surprise that DD has been deployed as a tool in drug discovery research. But even more than a tool,

DD has had a unique role in the conceptualization of novel drug treatments. The concept that LSD's particular, hallucinogenic effects may derive from a partial activation of 5-HT receptors, and the finding that none of the then available ligands was silent enough (40) to adequately antagonize LSD's DS effects (45), allowed us to conceptualize a new drug discovery project. The project's objective was to identify agents possessing an intrinsic activity low enough so as to be able to fully antagonize LSD and to not produce any generalization. It is in this manner that pirenperone was discovered (45,47) as a pure LSD antagonist acting as a particularly silent ligand at receptors for 5-HT (46) and, also, for DA and NA (49). Subsequent clinical studies indicated pirenperone to demonstrate improved antipsychotic activity over available neuroleptics, but with a short duration of action. The longer acting but similarly pure LSD antagonist and pirenperone derivative, risperidone (110, 111) became the first new chemical entity in 15 years to obtain FDA approval for the treatment of schizophrenia. Risperidone today stands as a prime instance of the so-called second generation antipsychotics succeeding chlorpromazine and haloperidol.

Loperamide (14) sets another example of DD-inspired drug discovery. It resulted from an effort to identify agents acting on opiate receptors that control gastrointestinal motility but that would be devoid of the subjective affects that opiates typically produce. Thus, DD has acted as a tool, but also as a source of concept, in drug discovery research.

TOLERANCE AND SIGNAL TRANSDUCTION

One early and most remarkable finding has been that tolerance does not develop to opiate drug discrimination (17,31). Although many other investigators have unanimously claimed that tolerance does develop (164), and while the matter has long remained controversial, a recent detailed analysis of the data (58) found no evidence to substantiate the development of tolerance.

If, as we argued, tolerance does not develop to opiate DD, and given that opiate DD emanates with exquisite specificity from the binding of adequate ligands to opiate receptors, how can it be that other opiate actions, such as analgesia, do demonstrate tolerance? Our answer to this question has been that tolerance does not develop to any opiate action. But then arises a new question; if tolerance does not develop to the primary action that opiates exert at their specific receptors, how then is it possible that some of the effects measured downstream of opiate receptor activation may at least appear to diminish under at least some experimental conditions? In an effort to account for these considerations, we devised a theory (37) that assumes that tolerance does not develop to the primary action of opiates, yet explains how some effects, such as analgesic effects, may appear to diminish. The theory also made the surprising prediction that chronic nociceptive stimulation should produce the inverse of apparent tolerance to opiate analgesia (i.e., should enhance the apparent analgesic effects). A further prediction was that chronic nociceptive stimulation and chronic opiate treatment, if matching, should act to neutralize each other's effects, so that opiates should provide a lasting relief of chronic pain. Experiments on opiate analgesia appeared to verify these predictions (34,38), and made us undertake a research effort that was aimed at validating the rat with adjuvant arthritic as an animal model of chronic pain (54).

The proposed, so-called System Theory (37) is about the fundamental, abstract mechanism whereby signal transduction occurs in biological systems. We recently reanalyzed (60) this theory in the light of the vast amount of technologically sophisticated evidence that is now available. We found that this theory provides a uniquely powerful account of tolerance as well as of dependence, addiction, and sensitization, explaining both the different definitions and the hallmark features of these phenomena.

A key feature of the theory is that it specifies that any instantaneous input is appreciated by its departure from the past activity that occurred over a certain time window called the sample period. This feature causes the transduction process to make any input generate two effects that are opposite in sign. The first-order effect results directly from the input's action on the substrate. The second-order effect results from the continual comparison of the instantaneous input that occurs at the later time with the mean past activity, which then incorporates the earlier impact. The proposed transduction process thus explains why opiates produce paradoxical effects (60); among these are the decrease as well as increase of adenylate cyclase, the increase and decrease of cyclic AMP formation, and the induction of both analgesia and pain. Similar paradoxes are found with countless other biological systems such as those involved in cell proliferation and cell death (60), suggesting these signal transduction mechanisms to be ubiquitous.

DRUG DISCRIMINATION: A PARADIGM OF NEURBIOLOGY

From this brief, cursory overview it would seem that DD over the past several decades has been, and in the future will continue to be, a particularly powerful paradigm of neurobiological research. More than simply constituting another technique of behavioral pharmacology or of neuropharmacology, DD studies have truly made pioneering contributions to such fundamental areas as partial receptor activation and signal transduction. By the very nature of its subject matter, the DD paradigm makes contributions to neurobiology that are unique, realizing as it does the astonishing feat of bridging "hard" molecular processes to the "soft" realm of subjectivity that at one point seemed forever beyond the reach of science.

One is left to wonder as to what it is that endows DD with this extraordinary resolving capacity. Part of the answer is that DD stands at a crossroads of several diverse disciplines, including molecular and cellular biology, biochemistry, physiology, psychology, and pharmacology. Another part of the answer may be that the paradigm most rigorously associates a well-defined molecular manipulation (e.g., opiate receptor activation) with one particular, well-defined behavioral response (e.g., the completion of an FR10 schedule of lever presses), brutally disregarding all other factors or even considerations that conceivably may intervene. A further, related part of the answer may be the alleged quantal nature of the DD response. Certainly, a quantaldependent variable represents the most unassuming of the different possible levels of measurement; it makes the least possible assumption as to the relationship that exists between the independent and the dependent variables that are being considered. The alleged quantal nature of the DD response has been criticized on grounds that graded measurements would enable more sophisticated analyses. However, quantal theories coherently encompassing molecular, pharmacological, and behavioral mechanisms have accounted for many findings that graded analyses have so far been left unexplained. It is interesting that even at the dawn of the third millenium the science of physics, in its attempt to account for the far simpler inorganic

matter, is in no position to abandon its quantal analysis of elementary particles. Thus, the extraordinary resolving capacity of the DD paradigm may perhaps relate to it involving an elementary particle of behavior (56).

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