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Pharmacology and Anxiety: Inadequacies of Current Experimental Approaches and Working Models

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BIGNAMI, G. *Pharmacology and anxiety: Inadequacies of current experimental approaches and working models.* PHARMACOL BIOCHEM BEHAV **29**(4) 771–774, 1988.—Current models concerning the mechanisms of punishment suppression and anxiolytic drug effects fail to account for several treatment-test interactions in pharmacological studies. This applies in the first place to some important "double dissociation" phenomena. For example, in rats benzodiazepines are effective in conflict tests (Geller- and Vogel-type) but not in go-no go avoidance discriminations, while the converse is true in the case of antimuscarinics. Such a situation makes it necessary to postulate a plurality of mechanisms which can serve punishment suppression in various conditions, and can operate at least partly "in parallel" rather than "in series." In addition, different varieties of a particular test can show quite different sensitivities to the same type of agent and/or different profiles in studies using various types of anxiolytics and antagonists. This does not preclude the use of one or the other test as a convenient assay. It appears, however, that we have only limited knowledge on the mechanisms involved in the production of behavioral effects which are assumed to be typical of the anxiolytic profile.

Anxiolytics Benzodiazepines Antimuscarinics Punishment suppression Conflict tests Avoidance discriminations

SINCE the classical studies of Masserman on ethanol and conflict, several types of punishment suppression have been used extensively as experimental anxiety models and for the assessment of anxiolytic drug effects. At first glance, these tests appear to have considerable specificity, as is shown by some well-known "double dissociation" phenomena. For example, agents with anxiolytic properties such as ethanol, barbiturates, meprobamate, and benzodiazepines selectively impair passive avoidance in Geller- and Vogel-type tests, while they affect active avoidance only at doses which block escape and produce gross motor incoordination. By contrast, classical neuroleptics selectively interfere with active avoidance while only exceptionally do they affect punishment suppression (for review and discussion see [1]).

EVIDENCE FOR A PLURALITY OF PUNISHMENT SUPPRESSION SYSTEMS

There are many inconsistencies in the data, however, which make that some important problems remain unsolved. In the first place, classical anxiolytics have been shown to be ineffective in rats in some types of punishment suppression which can be very sensitive to other agents; for example, in several active-passive avoidance tasks (discrete-trial go-no go discriminations). By contrast, scopolamine selectively disrupts passive avoidance in some of the latter tests, but is ineffective in conventional punishment suppression paradigms [1, 2, 4]. An example of the selectivity of these profiles is given in Fig. 1, showing (1) a marked disruption of passive avoidance by scopolamine in a go-no go shuttle-box task, which occurs in one of the feature negative discriminations (light-go, noise/light-no go) but not in that with a symmetrically opposite stimulus arrangement (noise-go, light/noise-no go), and (2) a remarkable absence or slightness of chlordiazepoxide effects on punished responses in this situation (for opposite results in punishment and conditioned suppression paradigms see e.g., [8,9]).

The interaction just mentioned and several others impose the preliminary inference that, depending on the task, response suppression can be served by different regulatory systems. These must operate at least partly "in parallel" rather than "in series," otherwise one should obtain asymmetrical, rather than symmetrical, dissociation phenomena.

In recent years, we have made several attempts to understand the conditions which lead to the use of one or the other punishment suppression system; the results so far obtained, however, have been largely negative. In one of these experiments, for example, rats were repeatedly exposed in the scopolamine state to the light-go, noise/light-no go discrimination until they compensated for the passive avoidance deficit caused by the treatment. (Remark that appropriate controls show that this desensitization is not a genuine pharmacological tolerance, but a form of relearning to cope with reinforcement requirements in spite of the drug-induced dysfunction; see [3,4].) The superimposal of drug challenges including chlordiazepoxide and amphetamine (also without effects of its own in this test) was

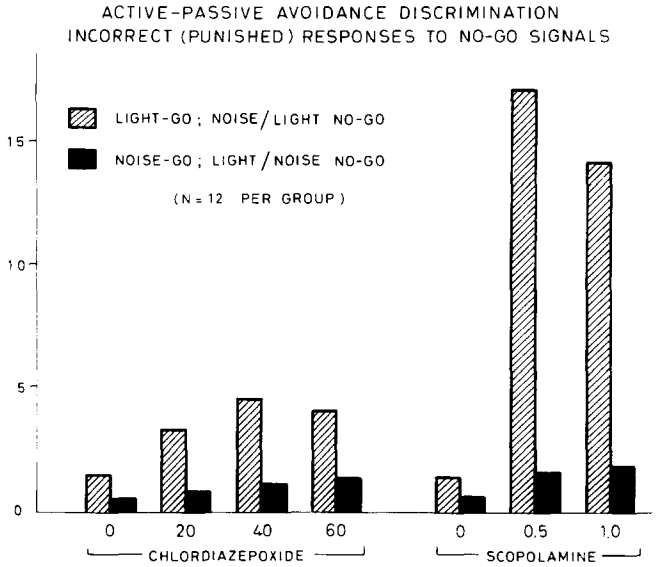

FIG. 1. Effects of chlordiazepoxide and scopolamine on the performance by rats of feature-negative go-no go avoidance discriminations with opposite stimulus arrangements. The bars indicate increases of punished responses to no go (passive avoidance) signals above control baselines (for procedural details see [10]). The data show marked scopolamine effects in one of the two tasks, and a remarkable lack of sensitivity to chlordiazepoxide of this type of punishment suppression. The sensitivity profiles of conflict tests (Geller- and Vogel-type) are just the opposite ("double dissociation;" see text). Reprinted from [2], by permission.

unable to impair passive avoidance after compensation of the scopolamine deficit. This prevents one from drawing any inference on the nature of the punishment suppression system(s) that are put to work in this particular situation under the constraint of central muscarinic blockade.

Even within a given type of task, the effects of a particular agent on punished responses can differ markedly. This applies for example to several versions of the CER (Estes-Skinner) paradigm, which show quite variable anxiolytic effects, and to the treatment-test interactions which determine the size and the direction of antimuscarinic effects on go-no go avoidance discriminations (see above and [1,4]). In other words, there is plenty of data to reinforce the notion that a plurality of suppression mechanisms which are largely independent from each other is available. This allows the organism to achieve punishment suppression by quite different "strategies," depending on the particular combination of organismic factors (species and strain; see below) and stimulus, response, and reinforcement variables.

In such a situation, insufficient attention has been so far given to those results which identify a critical discriminant determining whether or not a drug effect appears in a particular task. For example, typical benzodiazepine effects in a Geller-type conflict test do not occur when the duration of punishment periods is reduced [14]. In other words, benzodiazepine-sensitive suppression mechanisms are brought into play when the behavioral changes produced by punishment lead to extended delays of reward, but not when they produce shorter delays. This "choice" between punishment suppression strategies served by different mechanisms is clearly due to a joint role of positive and negative reinforcement events. In fact, benzodiazepine effects on alimentary behaviors *per se*, although substantial, can be ruled out as the only or the main determinants of the drugs' antipunishment action. The important role of the interactions between temporal and reinforcement variables in the production of benzodiazepine effects is also indicated by a variety of other studies; for example, the one showing a reduced tolerance to reward delays [13] and the one showing a passive avoidance deficit with distributed but not with massed practice, in a test which is antimuscarinic-sensitive independently of the practice variable [15].

More generally, the data so far mentioned deny that the effect of classical anxiolytics be at some "common link" or "final common path" in response suppression by aversive events. Comparable data from other types of experimental models, not involving the use of negative reinforcement, indicate that a similar conclusion applies to a variety of response changes which may, or may not, appear after benzodiazepine treatments; for example, to response enhancements in extinction and in discrimination tasks which cannot be analyzed here.

FUNCTIONAL LINKS WITHIN THE BENZODIAZEPINE-SENSITIVE SYSTEM

A second type of problem appears to be nested under the former one, since it derives from data obtained in tests selected on the basis of a high sensitivity to classical anxiolytics. Generally in agreement with the respective pharmacological-biochemical profiles, some of the newer agents show an anticonflict effect similar to that of the classical agents (for zopiclone and zolpidem see e.g., [5,11]), while other ones show little or no effect (for buspirone see e.g., [7,11]). On the other hand, it is difficult to understand some of the data obtained by the joint use of anxiolytics and antagonists, which are too complex to be discussed here in any detail. In brief, drug interaction profiles appear to depend not only on type of anxiolytic and type of antagonist, but also on the particular variant of punishment suppression test used in a given laboratory. This suggests that an apparent similarity of the effects of two different anxiolytics in different versions of a conflict test cannot be taken as evidence for an identity of drug action on the mechanisms serving punishment suppression.

The problems of analysis created by the interactions just mentioned may be quite different from those illustrated earlier, descending from the finding of double dissociation phenomena. In fact, it is almost tautological to state that various compounds with similar clinical properties, but with different pharmacological profiles, may act at different points of a functional chain within a given regulatory system. Therefore, at least part of the asymmetrical dissociation phemomena and differences in drug interactions may eventually be understood by a better knowledge on functional events and on sites and mechanisms of drug action (more "upstream" or more "downstream" within a given main system).

The same may apply to other apparent inconsistencies; for example, to the variable effects of several serotonergic agents in different tests selected for sensitivity to classical anxiolytics [6,12]. Little is known, however, about the effects of serotonergic agents on punishment suppression which is not affected by classical anxiolytics. (We have, in reality, unpublished data showing no effects of PCPA on the performance of passive avoidance by rats in the go-no go task which is maximally sensitive to scopolamine and little

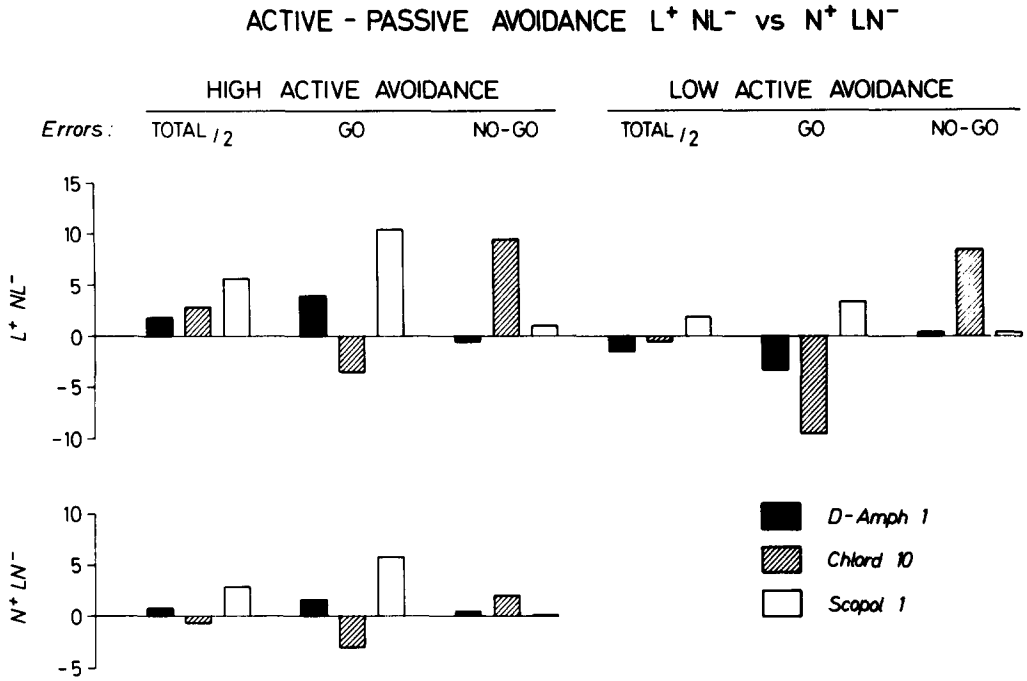

FIG. 2. Effect of d-amphetamine, chlordiazepoxide, and scopolamine on the performance of mice pretrained in go-no go avoidance discriminations like those of Fig. 1 (L^+NL^- = light-go, noise/light-no go; N^+LN^- = noise-go, light/noise-no go). The data refer to deviations from control baselines of active avoidance failures (go errors), passive avoidance failures (no go errors) and total avoidance failures (total errors halved to allow a direct comparison with the previous scores). All mice used in this experiment made few or no passive avoidance errors in control conditions. The data to the left refer to animals with a high active avoidance performance, and therefore, also a high discrimination performance. The data to the right are for animals with a low performance in active avoidance trials (L^+NL^- condition only, since the active avoidance performance was high in most animals in the N^+LN^- condition). Unpublished data from the author's laboratory.

sensitive to chlordiazepoxide. Other 5-HT system agents, however, have not been studied.) This makes it impossible to decide whether serotonergic drugs, when effective, act mainly on some component(s) in a benzodiazepine-sensitive system, or mainly by affecting a system which is at least in part separate from the former one.

METHODOLOGICAL IMPLICATIONS

The algorithm considering various possible outcomes is too complex to be summarized here. Intuitively, some combinations of these outcomes might require a mixed model of suppression mechanisms, with components operating partly in parallel and partly in series, and a wide range of functional patterns available to meet the demands of different situations. An important corollary appears to be that several alternative (and to some extent interchangeable) final common paths to suppression may be available. This is to account for the robustness of some types of punishment suppression in the face of all known drug and lesion treatments, at least after asymptotic performance is achieved. Although the universal negative cannot be proven, this inference is in agreement with the notion of an essential role of behavioral suppression in the economy of any organism.

The inconsistencies so far discussed show the need for behavioral, physiological-biochemical, and pharmacological work based on two types of strategies or working hypotheses. The first one is suggested by the finding of double dissociation phenomena which testify for the existence of different main regulatory systems working at least to a large extent in parallel, in spite of the apparent similarity of the behavioral end-points. Work in this area is made difficult by the frequent finding of higher-order interactions between organismic factors, such as species and strain, and a wide array of test factors. For example, recent work with mice trained in feature negative go-no go discriminations like those of Fig. 1 has yielded results which differ considerably from those obtained over and over again in many experiments with rats. On the one hand, responses in the noise-go, light/noise-no go task were little affected by scopolamine, chlordiazepoxide, and amphetamine, like in rats (lower part of Fig. 2). On the other hand, the profile of effects in the light-go, noise/light-no go task was opposite to that found in rats (upper left portion of Fig. 2). Passive avoidance failures (no go errors) were increased by chlordiazepoxide, which produced an apparently typical "antipunishment" effect. Scopolamine not only did not affect passive avoidance, but also produced a substantial impairment of active avoidance (increase in go errors). Additional data on low active avoidance mice (upper right portion of Fig. 2) showed both a facilitation of active avoidance and an impairment of passive avoidance by chlordiazepoxide, while scopolamine further depressed the former and did not affect the latter.

The second approach is the one that can exploit both the asymmetrical dissociation phenomena in tests selected for sensitivity to classical anxiolytics, and the different drug interaction profiles mentioned above. These findings testify for

the existence of several functional links within the benzodiazepine-sensitive system which await to be dissected more thoroughly.

These schemes are inevitably crude and may be only a first approximation in a process aimed at constructing more adequate working models. In fact, the real brain obviously combines in a much more complex fashion the two types of anatomical and functional arrangements (in parallel and in series), as is confirmed by the fact that both double (symmetrical) dissociation phemomena and asymmetrical dissociation phenomena are found when confronting different agents in different tests. However, the insufficient attention so far paid to the meaning of the phenomena just mentioned has resulted in the survival of models which have largely exhausted their heuristic potential, being unable to account for a substantial portion of the available data.

In conclusion, it appears that the research effort so far performed has been aimed at some admittedly important goals at the expense of others. In spite of several inconsistencies, for example, the work directed at the empirical validation of a wide variety of different anxiety models has produced many interesting results and helped considerably in the development of new types of agents. In addition, extensive physiological, biochemical, and pharmacological analyses have been performed within the test situations adopted by one or the other experimenter. But in spite of this effort, we are still far from understanding the critical behavioral determinants and processes which are responsible for differences in anxiolytic drug profiles and drug interactions, depending on organismic factors and test contingencies which lead to the reliance on different response control mechanisms. This prevents a more thorough assessment of the relations between results obtained in experimental models and clinical profiles. It also creates considerable uncertainties about what may be the more adequate strategies for the development of more effective and selective agents.

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