

SPECIAL INVITED ARTICLE/ARTÍCULO ESPECIAL INVITADO
**“BEHAVIOR-RELEASING” EFFECTS OF DRUGS:
ANTI-PUNISHMENT AND ANTI-CONFLICT
PROCEDURES**

*EFFECTOS LIBERADORES CONDUCTUALES DE LAS DROGAS:
PROCEDIMIENTOS DE ANTI-CASTIGO Y ANTI-CONFLICTO*

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ABSTRACT

Anxiolytic drugs are said to reduce internal states (e.g., anxiety) that are induced by the presentation of aversive events, leading to a release of behavior that has been suppressed. The objective of the present paper is to discuss two categories of procedures that are often used interchangeably-- anti-punishment (procedures that release punished behavior) and anti-conflict (procedures that reduce avoidance behavior). Similarities and differences between the two categories of procedures are reviewed, emphasizing distinctions between theoretical, methodological, and pharmacological specifics. The anxiety-as-explanation issue is discussed also, in terms of possibly obscuring the behavioral and pharmacological mechanisms that are involved with drugs that “release” behavior.

Key words: anxiolytic drugs, anti-punishment, anti-conflict, anxiety, explanation, behavioral mechanisms, pharmacological mechanisms.

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RESUMEN

Se ha dicho que las drogas ansiolíticas reducen estados internos (e.g., ansiedad) que son inducidos por la presentación de eventos aversivos, y llevan a la liberación de conducta que ha sido suprimida. El objetivo del presente artículo es discutir estas dos categorías de procedimientos que con frecuencia se usan de manera intercambiable -- anti-castigo (procedimientos que liberan conducta castigada) y anti-conflicto (procedimientos que liberan conducta de evitación). Se revisan las semejanzas y diferencias entre las dos categorías, haciendo énfasis sobre detalles teóricos, metodológicos y farmacológicos. También se discute el problema de la ansiedad como explicación, en términos del posible oscurecimiento que tal explicación produce sobre los mecanismos conductuales y farmacológicos involucrados en las drogas que "liberan" conducta.

Palabras clave: *liberación de conducta, drogas, anti-castigo, anti-conflicto, ansiedad, explicación, mecanismos conductuales, mecanismos farmacológicos.*

Anxiolytic (anxiety-reducing) drugs have been shown to selectively "release" behavior that has been suppressed. The basic procedure involves a choice between two alternatives. One alternative consists of a simultaneously appetitive and aversive condition (also known as conflict), for example, the concurrent delivery of food and shock. The second alternative consists of avoidance of the first alternative, i.e., engaging in "other" behavior. Under non-drug conditions, the human or animal tends to engage in the latter alternative. Under the anxiolytic drug, the former alternative is more influential on behavior, presumably because behavior is less sensitive to the aversive condition.

In the behavioral pharmacological literature, the terms *anti-punishment* and *anti-conflict* are used to describe drug effects on behavior under approach-avoidance types of procedures. The terms are often used interchangeably (see, for example, Fontana, Carbary, & Commissaris, 1989; Koek & Cobpaert, 1991; Lerner, Feldon, & Myslobodsky, 1980; Pattij, Hijzen, Gommans, Maes, & Olivier, 2000; Thiebot, Soubrie, & Simon, 1985; Waddington & Olley, 1977), although on close inspection, important differences exist between the categories of the procedures. Anti-punishment effects refer to a drug-induced increase in behavior that specifically has been punished within the laboratory setting. Typically, a baseline response rate of lever-pressing or other free operant is established under a schedule of food reinforcement. Electric current, or some other aversive stimulus, is then delivered under a schedule of punishment, reducing the rate of lever-pressing relative to the unpunished baseline. Alternative behavior, such as exploring or grooming, becomes more

probabilistic. The anti-punishment effects of an anxiolytic drug are evident when an increase in behavior suppressed by punishment is observed, and this increase is independent of an increase in response rate in the unpunished baseline.

In anti-conflict procedures, an organism is presented with a situation that has both aversive and appetitive properties, though they are less clearly specified than in anti-punishment procedures. Under non-drug conditions, the animal does not engage in the task, but when specific types of anxiolytic drugs are administered, the animal may engage in the task more frequently. For example, in the light-dark task a box is split into two compartments; one half is illuminated and one half is not. Under control conditions, rodents spend more time in the darkened area of the light-dark test box and are also less active in the illuminated portion of the box than in the darkened portion. Some anxiolytics appear to increase selectively the amount of time in illuminated areas. There is no experimental induction of punishment in the anti-conflict situation, but anti-conflict is similar to anti-punishment in that behavior that occurs at a low probability is released by the drug.

The tendency to confuse the terms anti-punishment and anti-conflict procedures likely comes from the common practice of categorizing and discussing these procedures as animal (and human) models of anxiety. The conceptualization goes as follows: Engaging in a situation that is simultaneously appetitive and aversive induces anxiety or discomfort, and the administration of the drug is said to remove the subjective anxiety or discomfort. Hence, the mechanism for behavioral change is removal of anxiety or discomfort. In some instances, the mechanism refers to a disengaging of a behavioral inhibition system (BIS; Gray, 1988). The drawback is that conceptualizing anxiety or the BIS as the explanatory mechanism has attenuated the search for behavioral mechanisms involved with anxiolytic drugs, which may include, for example, a drug-induced decrease in behavioral sensitivity to the aversive condition or perhaps a drug-induced increase in behavioral sensitivity to the appetitive condition. (Gray, 1988, specifies three possible anxiolytic mechanisms: behavioral inhibition, preparation for vigorous action, and increased attention to the environment. However, the specific mechanisms of *behavior* for those three suggestions are not clearly defined.) MacCorquodale and Meehl (1948) warned that the use of labels, such as anxiety, can lead to construct reification; that is, the term becomes explanatory (or used as a real cause) instead of descriptive, as it was originally intended. Moreover, the singular focus of anxiety as an explanatory variable has halted the discussion of behavioral differences between anti-conflict and anti-punishment procedures. This is interesting since some drugs have differential effects across procedures, suggesting different neurochemical substrates that might underlie two different behavioral processes, as opposed to two different types of anxiety as

some researchers suggest (see, for example, Stefanski, Paleiko, Kostowski, & Plaznik, 1992). The purpose of this paper is to describe and summarize the literature on the releasing function that anxiolytic drugs have on behavior, and to elucidate the differences between anti-punishment and anti-conflict procedures. Additionally, the place of anxiety in anti-conflict and anti-punishment will be critiqued.

ANTI-PUNISHMENT

Anti-punishment effects are generally observed with drugs that are GABA agonists, such as barbiturates, benzodiazepines, and alcohol; opiates, stimulants, and other drugs do not generate anti-punishment effects. There is some inconsistent evidence that some serotonergic drugs (often used for the treatment of mood disorders) also have anti-punishment effects. These drugs effects will be reviewed later.

Anti-punishment effects have been demonstrated across a variety of species, including rats (e.g., Koob, Braestrup, & Britton, 1986; Vogel, 1980), squirrel monkeys (e.g., Barrett, Brady, & Witkin, 1985), cats (e.g., Masserman & Yum, 1946), pigeons (e.g., Brocco, Koek, Degruyse, & Colpaert; Koek & Coelpaert, 1991; Mansbach, Harrod, Hoffman, Nader, Lei, Witkin, & Barrett, 1988), and humans (e.g., Carlton, Siegel, Murphee, & Cook 1981; Rasmussen & Newland, 2006). These effects have been observed across a variety of procedures, as well. These procedures are summarized in Table 1 and discussed below.

Conjoint Schedules of Reinforcement and Punishment and Conditioned Suppression

Barrett, Brady, & Witkin (1985) placed lever-pressing of squirrel monkeys under a conjoint fixed interval 3' fixed ratio 30-shock schedule, such that the first response that occurred after every 3 min elapsed was reinforced with liquid reinforcement or a banana chip. In addition, every 30th response was punished with shock, and this contingency suppressed response rate. Doses of the GABAergic compounds chlordiazepoxide (1-60 mg/kg), pentobarbital (3-10 mg/kg) and ethanol (1-2.5 g/kg) increased punished response rates similarly (between 125 and 225% of punished control rates), but did not increase unpunished responding. Comparably strong anti-punishment effects have been replicated with chlordiazepoxide (Mansbach, Harrod, Hoffman, Nader, Lei, Witkin, & Barrett, 1988; Witkin, Mansbach, Barrett, Bolger, Skolnick, & Weissman, 1987) under similar schedules of reinforcement and punishment. Moderate anti-punishment effects have been observed under buspirone (Witkin, Mansbach, Barrett, Bolger, Skolnick, & Weissman, 1987), gepirone, clo-

Table 1. Summary of studies demonstrating anti-punishment and anti-conflict effects.

<i>Procedure</i>	<i>Strong Effects Shown with These Drugs</i>	<i>Neurochemical Mechanism</i>
<i>Anti-punishment Studies</i>		
Conjoint schedule	ethanol, chlordiazepoxide, pentobarbital	GABA
Vogel procedure	chlordiazepox., diazepam, oxazepam, meprobamate, phenobarbital, secobarbital, pentobarbital, ethanol, alprazolam, midazolam	GABA
Conditioned Suppression	alprazolam, perphanazine, chlordiazepoxide, propranol, phenobarbital, secobarbital, pentobarbital, ethanol, diazepam	GABA
Geller-Seifter procedure	chlordiazepoxide, diazepam, meprobamate, phenobarbital, pentobarbital	GABA
Multiple schedule	amobarbital, chlordiazepox., pentobarbital; ethanol; phenobarbital, secobarbital	GABA
Concurrent schedule	chlordiazepox., diazepam, ethanol	GABA
<i>Anti-conflict Studies</i>		
Elevated Plus Maze	Diazepam, ethanol	GABA
Light-dark cage	Diazepam, ethanol	GABA
	ipsapirone, PAPP, (-)MDL 72832, (+) MDL 72832, buspirone, ICS 205-930	5-HT
"Taboo" behavior (e.g., aggression)	chlordiazepoxide, ethanol	GABA
<i>Other (e.g., open field activity, six-foot alley, ethological)</i>	chlorpromazine diazepam, fluoxetine, buspirone, mainserin, gepiron	DA antagonist GABA 5-H

zapine, and 8-OH-DPAT (Mansbach, Harrod, Hoffman, Nader, Lei, Witkin, & Barrett, 1988), all of which are serotonergic agonists.

Dworkin, Bimle, & Miyauchi (1989) found results similar to the above-mentioned anti-punishment studies after placing bar-pressing under a random ratio (RR) schedule of reinforcement, in which a probability generator randomly determined whether the response would be reinforced after a number of lever presses. Rats pressed an average of 55 responses per minute under this schedule. Then a RR schedule of shock was superimposed on the reinforcement schedules, and this suppressed bar-pressing by an order of magnitude. Low doses of pentobarbital (5.6 and 10 mg/kg) increased rates of punished responding by five to 10 times, but did not increase unpunished responding. Cocaine, which normally increases low rates of responding maintained by reinforcement, did not produce anti-punishment effects.

Operant licking also has been used for examining anti-punishment effects with conjoint schedules of reinforcement and punishment, and this is often referred to as the Vogel procedure (after Vogel, Beer, & Clody, 1971). Here, water-deprived rats make contact with a spout that produces water or some other liquid under a continuous reinforcement schedule. Once the licking comes under the control of the liquid reinforcer, licking is punished by delivery of electric current under a schedule of punishment. In the original study, Vogel, Beer, and Clody (1971), programmed a fixed ratio 20 (FR20) schedule of shock (every twentieth lick produced a shock) and licking was suppressed to low levels. The GABAergic compounds chlordiazepoxide (6 and 8 mg/kg), diazepam (2 and 4 mg/kg), oxazepam (3 to 12.5 mg/kg), meprobamate (30 to 120 mg/kg) and pentobarbital (5 and 10 mg/kg) dose-dependently increased the rates of punished, but not unpunished, licking. *d*-Amphetamine (a catecholamine agonist), pemoline (an epileptic) and scopolamine (a cholinergic antagonist) produced no anti-punishment effects. Similar anti-punishment effects with the Vogel task have been replicated with diazepam (e.g., Liljequist and Engel, 1984; Stefanski, Palejko, Kostowski, & Plaznik, 1992) and chlordiazepoxide (e.g., Brocco, Koek, Degruyse, & Colpaert; Kennet, Trail, & Bright, 1998), and have been found with other GABAergic compounds, such as alprazolam (Kennet, Trail, & Bright, 1998), midazolam (Stefanski, Palejko, Kostowski, & Plaznik, 1992), and ethanol (Liljequist and Engel, 1984; Vogel, 1980). Buspirone yields conflicting data in which anti-punishment effects are inconsistently demonstrated, but when they are, they are moderate at best (cf. Kennet, Trail, & Bright, 1998; Schefke, Fontana, & Commissaris, 1989; Stefanski, Palejko, Kostowski, & Plaznik, 1992). Ritaserin, ipsarone, and various other serotonergic drugs were shown to increase punished responding to a moderate extent (Stefanski, Palejko, Kostowski, & Plaznik, 1992); however it is unclear whether this increase was specific to punished responding, because data on unpunished responding were not shown. Hence, it is uncertain whether these were true anti-punishment effects, or are able to be explained by other behavioral mechanisms, such as rate dependence.

Operant licking also has been used to examine anti-punishment effects within the context of the conditioned suppression procedure (see Estes & Skinner, 1941). In the conditioned suppression procedure, an aversive, usually shock, is paired with a stimulus. The presentation of the conditioned aversive stimulus alone (without the shock) induces a suppression of behavior, relative to the absence of the conditioned stimulus. Conditioned suppression of bar-pressing and conditioned suppression of drinking (CSD), in which the operant is licking a water spout, has been demonstrated with diazepam (Commissaris, Harrington, & Altman, 1990; Kilts, Commissaris, McCloskey, Damian, Brown, Barraco, & Altman, 1990; Commissaris & Rech, 1981; McCloskey, Paul, & Commissaris, 1987; Mokler & Rech, 1985), al-

prazolam (Commissaris, Harrington, & Altman, 1990); phenobarbital (Commissaris, Vasas, & McCloskey, 1987; Commissaris, McCloskey, Damian, Brown, Barraco, & Altman, 1990; McCloskey, Paul, & Commissaris, 1987), pentobarbital (Commissaris, Vasas, & McCloskey, 1987), and secobarbital (Commissaris, Vasas, & McCloskey, 1987), all of which are GABAergic.

Multiple Schedules of Reinforcement and Punishment

A multiple schedule involves two schedules of reinforcements that are alternately placed in effect, each signaled by a different stimulus. Geller and Seifter (1960) used the multiple schedule to study anti-punishment effects by programming a simultaneous schedule of punishment and reinforcement in one component and comparing behavior to a second component with no punishment schedule. The advantage the multiple schedule has over the simple schedule is that unpunished and punished behavior can be examined readily within a single session for each subject. In Geller and Seifter's (1960) study, the bar-pressing of rats was placed under a multiple variable interval (VI) 2'-- continuous reinforcement (CRF) plus shock schedule. In the VI 2' component, the first response after an average of 2 minutes elapsed, produced a reinforcer. Under the CRF plus shock component, every response produced a food pellet and a shock, thereby suppressing lever-pressing in that component only. A single dose (120 mg/kg) of meprobamate increased the number of lever-presses in the CRF component by an order of magnitude (control mean=3.22, meprobamate mean=33.67). Lever-press increases were not observed in the VI (unpunished) component. Phenobarbital and pentobarbital dose-dependently increased the number of punished, but not unpunished, responses as well. Promazine (an antipsychotic) and d-amphetamine *decreased* the number of punished responses, again showing anti-punishment effects that are specific to anxiolytic drugs. In a later study, the Geller-Seifter procedure was used to show that reserpine, a depressant that acts by depleting norepinephrine and serotonin (5-HT), revealed anti-punishment effects, but morphine, an opiate, did not (Geller, Bachman, & Seifter, 1963.) The lack of effect to morphine is important because it indicates that anti-punishment effects are not related to analgesia.

Other studies have replicated anti-punishment effects with multiple schedules across a variety of parameters, including the type of aversive stimuli. Several studies found that chlordiazepoxide and pentobarbital increased punished responding when timeout (Branch, Nicholson, and Dworkin, 1977; McMillan, 1967; van Haaren and Anderson, 1997) and pressurized air (Spealman, 1979) were used as aversive stimuli. Anti-punishment effects revealed by the Geller-Seifter procedure have also been found with other GABAergic compounds, including amobarbital (e.g., Davidson and Cook, 1969; Morse,

1964), chlordiazepoxide (e.g., Glowa and Barrett, 1976; Koob, et al., 1986; Sethy and Winter, 1972), ethanol (e.g., Koob, et al., 1986; Glowa and Barrett, 1976), phenobarbital (e.g., Commissaris, Vasas, and McCloskey, 1988), and secobarbital (e.g., Commissaris, Vasas, and McCloskey, 1988). These effects have been observed also with chlorpromazine (Dinsmoor and Lyon, 1961), an anti-psychotic dopamine antagonist, though this drug has inconsistent findings associated with anti-punishment (cf. Morse, 1964; Pollard & Howard, 1979, for example).

Concurrent Schedules of Reinforcement

The concurrent variable interval variable interval (*conc VI VI*) schedule of reinforcement has been used to examine anti-punishment effects in the context of choice behavior. Here, responding under two simultaneously available schedules of reinforcement produces reinforcers that are delivered at an overall predictable rate, although the moment-to-moment deliveries vary. Behavior allocation between the two alternatives matches the relative reinforcement rates (e.g., Herrnstein, 1961). In other words, if twice as many reinforcers are delivered from alternative A than alternative B, twice as much behavior will be allocated to alternative A than alternative B. Aversive stimuli, such as shock, have been used with this procedure in an effort to examine how punishment affects behavior allocation (e.g., Wojnicki & Barrett, 1993). With humans, less noxious stimuli, such as noise (e.g., Katz, 1973) or point and money loss (e.g., Bradshaw, Szabadi, & Bevan, 1979; Critchfield, Paletz, & MacAleese, 2003; deVillers, 1980; Rasmussen & Newland, 2006) have been used. The concurrent schedule is useful in studying punishment effects because if behavior under one alternative is punished, the behavior of the unpunished alternative is available for allocation. Behavior, then, can be “captured” under the unpunished alternative. When punishment is superimposed on simple or multiple schedules of reinforcement, the probability of interacting with the key, bar, or whatever is associated with punishment is lowered and alternative behavior is more probable. The precise measurement and recording of “other” behavior that occurs in place of punished behavior (e.g., cage exploration, grooming, sleeping or sniffing) is difficult. The only dependent variable an experimenter has to examine in terms of free-operant behavior is the very few responses that occur toward the key or lever. With concurrent schedules, the environment is arranged in such a way that behavior toward the unpunished alternative can occur (i.e., the rat, for example, can still lever-press for reinforcers instead of grooming or exploring.) Within the context of studying anti-punishment effects, it is important because it is possible to examine concurrently an unpunished and punished condition—the putative “litmus test” for specificity.

Anti-punishment effects have been explored using concurrent schedules.

Wojnicki and Barrett (1993) conducted a study with a *conc VI VI* schedule that included a superimposed schedule of punishment on one alternative. They examined behavior in the punished and unpunished alternatives under varying doses of chlordiazepoxide, buspirone, and *d*-amphetamine. Responses under the punished component increased in a dose-dependent fashion under chlordiazepoxide and buspirone, but not under amphetamine. Behavior under the unpunished component decreased slightly at higher doses for the two anxiolytics, and decreased under amphetamine. Sepinwall, Grodsky, and Cook (1978) found similar results under concurrent schedules with squirrel monkeys and the drugs diazepam and chlordiazepoxide. Anti-punishment effects have been demonstrated under concurrent schedule with humans with the drugs diazepam (Carlton et al., 1981) and ethanol (Rasmussen & Newland, 2006).

ANTI-CONFLICT

As mentioned previously, anti-conflict studies involve examining behavior under a simultaneously appetitive (approach) and aversive (avoidance) condition, broadly defined. An anxiolytic drug functions to increase avoidance behavior. The following procedures represent anti-conflict studies, and are meant to be an illustrative, not exhaustive, reflection of the extant literature.

Elevated-Plus Maze

In the elevated plus maze two long planks bisect each other at 90 degree angles. The bisection is usually enclosed as a small compartment. Two of the four protruding arms are enclosed within walls and the other two are exposed. A rodent, usually a rat, is placed in the center compartment and the arms are available for exploration. Under non-drug conditions rats tend to traverse the enclosed arms more often and to a greater extent than the exposed arms (Montgomery, 1955). Several studies have shown that GABAergic drugs, such as diazepam (e.g., Balfour, Graham, & Vale, 1986; Moser, 1989) and ethanol (e.g., Lister, 1988) selectively increase open-arm exploration and time spent in the exposed arm. Some atypical anxiolytics (5-HT agonists), such as ipsapirone, PAPP, (-)MDL 72832, and (+)MDL 72832 also increase open arm entries (Moser, 1989). However, buspirone has been found to *decrease* open-arm entries (Moser, 1989; Pellow, Johnston, & File, 1987).

Light-Dark Task

Recall in the light-dark task, under non-drug conditions, a rodent may allocate more time in the dark compartment of a light-dark box and avoid the light compartment. Benzodiazepines may increase entries and time spent in the light compartment. For example, Onaivi and Martin (1989) reported that under control conditions, mice were more active in a dark chamber, even when it was smaller or equal in size to a light chamber. Some doses of diazepam and buspirone, but not amphetamine and morphine, significantly increased the exploratory activity in the light cell, and did not increase activity in the dark cell. These findings have been replicated with diazepam (Costall et al., 1987) and found with ethanol (Belzung, Misslin, and Vogel, 1988; Costall et al., 1987).

Other Procedures

Anti-conflict effects also have been reported in open field activity, in which food (the appetitive stimulus) is placed in an open field. Here, the putative competing forces are said to be food and neophobia (the aversive stimulus, especially if the environment is brightly lit). Bodnoff, Suranyi-Cadotte, Quiron, and Meaney (1989) reported decreased latencies to contact with food when rats were chronically administered a variety of drugs, including diazepam, fluoxetine, buspirone, mainserin, and gepirone. Interestingly, the decreases in latencies were selective to anxiolytics (diazepam and buspirone) *and* anti-depressants (fluoxetine, mainserin, and gepirone). However, these findings are limited because there was no test for the selectivity of aversive versus appetitive conditions, since the inferred drives were untestable. Moreover, only a single dose of each drug was used, so complete dose-response profiles for each drug were not obtained.

The six-foot alley is another conflict procedure in which anti-conflict effects have been demonstrated. Grossman and Miller (1961) conducted a study in which food was placed at the end of a six-foot alley. Each foot was then associated with a progressively larger increase in shock intensity, such that no shock was correlated with the first foot and the largest intensity shock (180 volts) was associated with the sixth foot. Traversing speed within each one-foot length was recorded under both shocked and non-shocked conditions. Chlorpromazine and ethanol increased speed in each one-foot component under shocked, but not non-shocked conditions.

Studies that examine “taboo” behavior with humans may qualify as anti-conflict studies. One procedure is the slide rate measure in which slides with sexual, aggressive, or neutral themes are presented to participants. Under ethanol, participants spend more time than under non-drug conditions watching those of a sexual or aggressive, but not neutral, nature than under non-drug conditions (Kallmen & Gustafson, 1998). Here, the putative competing forces are said to be the “inherently” reinforcing nature of sex or violence

versus the socially punishing contingencies of viewing pornographic or violent images, which the subjects supposedly bring with them to the experiment.

Aggression in humans is another taboo behavior that may apply to anti-conflict. Dougherty, Cherek, and Bennett (1996) examined the number of aggressive responses by women that occurred under different doses of ethanol. Participants could push a button to earn points exchangeable for money. They could also push another button to take points from another "person," which was interpreted by the authors as an aggressive response. To induce aggressive responses, subjects were told that every time their counters lost a point it was because a person in another room took the point. The number of aggressive responses increased with ethanol dose, and under the highest dose of ethanol (1 g/kg) aggressive responses doubled. The number of point-earning responses did not increase under ethanol. Although there was no punishment condition in this study to suppress behavior, the findings may qualify as anti-conflict because aggressive responding occurred at lower rates initially. This finding might imply that extra-experimental contingencies may serve to punish behavior, and the participants brought this history with them to the laboratory. Similar results have been reported with male participants (see Cherek & Steinberg, 1987; Cherek, Steinberg, and Manno, 1985; Cherek, Steinberg, & Vines, 1984) and seem to be specific to ethanol, as d-amphetamine (Cherek, Steinberg, & Kelly, 1986), caffeine (Cherek, Steinberg, & Brauchi, 1983), and nicotine (Cherek, 1981) produced behavioral changes that were not specific to aggressive responding.

COMPARING ANTI-PUNISHMENT AND ANTI-CONFLICT PROCEDURES

Anti-conflict is similar to anti-punishment in that behavior that occurs at a low frequency under non-drug conditions selectively emerges during drug conditions. The difference between conflict and punishment, however, rests on several important details. In conflict procedures the reinforcement contingencies are poorly defined-- behavior often is discussed as the resolution of "two opposing motivational forces" (p. 443; Commissaris, 1993). For example, in the light-dark task, the appetitive condition is defined as the animal's drive to explore and the aversive condition as its innate tendency to avoid light (Commissaris, 1993). One can identify the problem of subjectivity and anthropomorphism that may arise from defining the conditions as such. More important, other problems are evident in using such characterizations, such as assumptions of a behavioral history, (more specifically, a history of punishment) and the inability to observe stability in behavior. Punishment procedures, conversely, rely on simple and easily interpretable characterization of

punished and unpunished behavior, though they certainly could be framed within a “conflict” definition.

A second difference between the two types of procedures is that anti-conflict procedures tend to rely on more naturalistic behavioral repertoires of the subjects studied, for example, approach to darkness, exploring, aggression, etc. Anti-punishment studies (with the exception of licking) involve arbitrary responses with aversive stimuli that are unlikely to be a part of an organism’s natural environment (e.g., shock). Hence, anti-conflict procedures can be argued to have more ecological validity and generalization to the real world, while anti-punishment procedures can be argued to result in more precise definition of the variables and tighter control of the experimental environment, resulting in more internal validity. Consideration of both types of procedures is essential for a fuller characterization of behavior under anxiolytic drugs, but to categorize anti-punishment and anti-conflict as interchangeable is inaccurate.

A third difference between the sets of procedures is that under punishment behavior is characterized *first* within the unpunished (“approach”) conditions (i.e., baseline), and *then* the aversive stimulus is delivered as a punisher, allowing a situation in which specificity is easily interpretable. Conflict *assumes* that some conditions are aversive and others are appetitive, based on the animals’ behavior upon first experience, but without showing this in a functional manner. In some procedures (for example, open field activity), there is no built-in test for specificity of appetitive versus aversive conditions.

A fourth difference, and probably the most compelling, is that anti-punishment involves behavior that specifically has been punished, and anti-conflict is one that likely involves avoidance, or negative reinforcement—these two phenomena have different behavioral and pharmacological mechanisms. Behaviorally, punishment reduces behavior by the presentation of an aversive stimulus and negative reinforcement *increases* behavior by the *removal* of an aversive stimulus. As discussed, and as shown in Table 1, pharmacologically, anti-punishment effects have been identified specifically with GABAergic drugs, namely benzodiazepines, barbiturates, and alcohol and less so with serotonergic ones; anti-conflict effects have been related to GABAergic compounds, a much wider variety of 5-HT agonists (second-generation anxiolytics), dopaminergic agonists, and some other drugs that do not necessarily have anxiolytic properties (such as 5-HT antagonists and nicotine).

Studies on the neurochemical basis of negative reinforcement using procedures other than anti-conflict suggest that a wider range of neurotransmitter systems seems to be involved in negative reinforcement. Shock-maintained behavior, in which postponement of shock maintains the response that produces the shock postponement, is an example. Two-factor theorists argue that the maintenance of the response involves escape from anxiety or fear as-

sociated with time nearing the delivery of the aversive event (Mowrer, 1947). (The debate on one- and two-factor theories of avoidance is captured nicely in an amalgam of commentaries of the May 2001 issue of the *Journal of the Experimental Analysis of Behavior*.) In line with two-factor theory, then, drugs that are said to reduce anxiety should result in a decrease in shock-maintained avoidance responses (without disabling motor function). The anxiolytics buspirone (Galizio, Hale, Librorio, & Miller, 1993), diazepam (Kuribara, 1978), pentobarbital (Kuribara, 1978), and ethanol (Galizio, Perone, & Spencer, 1986) have been shown to decrease shock-maintained avoidance responses. However, other anxiolytics, such as chlordiazepoxide and 8-OH-DPAT (Galizio, Hale, Librorio, & Miller, 1993) have been shown to *increase* shock-maintained avoidance responses. In addition, some muscarinic agonists and dopamine antagonists, also known as anti-psychotics, have reduced conditioned shock avoidance responses in discrete trials procedures (Shannon, *et al*, 1999). Moderate doses of the anti-psychotic chlorpromazine have been shown to decrease also free operant shock-maintained avoidance responses (Galizio, Journey, Royal, & Welker, 1909; van Haaren, & Zarcone, 1994), though avoidance responses increased at low doses. It seems, then, that when it comes to shock-maintained responses, the role of anxiety, as referenced by response to anxiolytics, is not central or straightforward.

Anxiolytics that affect other event-maintaining responses (in addition to shock) have been examined. Responses that produce signaled timeout from avoidance have been shown to decrease with administration of buspirone. However, opiate agonists, including morphine, methadone, fentanyl, and U50-488 also decrease avoidance responses (Galizio, Robinson, & Ordroneau, 1994), though the opiates also increased shock-maintained avoidance, but to a lesser extent than timeout. These data, combined with the puzzling data on the behavioral pharmacology of shock-maintained avoidance suggests that procedural variants such as the event itself that maintains avoidance (e.g., timeout, shock avoidance, escape from a conditioned stimulus), rather than anxiety or fear, may be a play a key role in understanding the maintenance of avoidance. In other words, if anxiety was the internal stimulus that was reduced with anxiolytic drugs, the same anxiolytic drugs should reduce avoidance responses in an avoidance task, despite what type of aversive event maintains the behavior. Moreover, only drugs that have been shown to be anxiolytic should decrease avoidance responses; anti-psychotics and muscarinic agonists should not. It may well be the case that the type of event that maintains the response in avoidance is a non-trivial matter in terms of examining drug effects. Consider Verhave's (1962) view of timeout from avoidance, which suggests that timeout may function more as a positive reinforcer (addition of a safety stimulus) as opposed to a negative reinforcer. Views such as these (as opposed to appealing to anxiety as explanation) are more likely to

lead to better formulated hypotheses about how drugs will affect a behavior, and will likely lead to a clearer understanding of drug-behavior interactions.

It seems then, that the pharmacological mechanism of negative reinforcement is not straightforward. The behavioral and pharmacological mechanisms of negative reinforcement may depend on such parameters as the event maintaining the behavior, event-independent factors (e.g., rate dependence—see Galizio and Allen, 1991), as well as some possible species differences (which may make members of one species more sensitive to the aversive or reinforcing properties of particular events, e.g., light). These parameters may involve different and multiple neurochemical substrates that when taken together would result in a nebulous and confusing picture, but when examined independently, may provide a clearer picture of the pharmacological basis of negative reinforcement.

It seems clear, though, that behavior maintained by negative reinforcement is pharmacologically (and behaviorally) different from behavior maintained by punishment. Anti-punishment effects hold to GABA related drugs, which likely function to make behavior less sensitive to the punishing contingency. The negative reinforcement nature of anti-conflict procedures holds to a larger range of drugs that may not fit neatly into the anxiolytic pharmacological class. Indeed, the picture with anti-conflict procedures is much more complex than that of anti-punishment. Moreover, the common internal mechanism of anxiety reduction as an explanation for the drug's efficacy in releasing suppressed behavior does not seem to be supported pharmacologically between the two categories of procedures. Indeed if anxiety reduction was the mechanism for behavioral change with anxiolytic drugs, there would be a greater overlap in drugs that affect behavior under anti-punishment and anti-conflict procedures. Because anti-punishment and anti-conflict procedures are distinct in terms of the behavioral mechanisms and pharmacological mechanisms involved, it makes little sense to classify them in an interchangeable manner.

Conclusions

Recently, anti-conflict, and some anti-punishment procedures have been used to disentangle 5-HT receptor subtypes (e.g., Dhonnchadha, Hascoet, Jolliet, & Bourin, 2003), and to compare anti-conflict/anti-punishment effects to discriminative properties of the drugs (e.g., McMillan, Li, & Hardwick, 1997; Pattij, Hijzen, Maes, & Olivier, 2000.) The latter represents a step in the right direction for behavior analysis, because the question that arises from comparing discriminative and anti-conflict/anti-punishment properties is whether the stimulus properties of a drug are necessary to disrupt the behavior-releasing effects of a drug. In other words, perhaps the behavioral mechanism for anti-conflict or anti-punishment has to do with yet another behavioral mechanism,

in addition to event-dependent (or event-independent) effects--the internal stimulus properties that may, or may not exert influence on punished behavior or negatively reinforced behavior. Hypotheses of the relation between the discriminative properties and the behavior-releasing effects of anxiolytic drugs suggest that the neurochemical substrate underlying the two mechanisms may have some similarity (Pattij, et al, 2000). Answers to these questions may become clear as more studies are conducted.

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