Same or Different? An exploration of the behavioral effects of benzamides

¿Igual o diferente? Una exploración de los efectos conductuales de las benzamidas[1]

Marc Richelle[2]

University of Liege, Belgium

ABSTRACT

Modern research in behavioral pharmacology involves the evaluation of new compounds, searching for similarities with some reference drugs. However, to detect possible unexpected effects, one should look for different rather than similar effects, with respect to known drugs. In the present paper, the behavioral effects of two benzamides, namely sulpiride and tiapride, are evaluated, stressing the features that differentiate them from other drugs. Rats and cats were employed as subjects and performance was maintained by several aversive and positive reinforcement schedules. The benzamides explored do not fit simply into the classificatory frames of present day psychopharmacology, since several differences were evident with respect to the behavioral effects of well known compounds.

DESCRIPTORS: Behavioral pharmacology, benzamides, rats, cats.

RESUMEN

La investigación moderna en farmacología conductual involucra la evaluación de nuevos compuestos, buscando semejanzas con algunas drogas de referencia. Sin embargo, para detectar posibles efectos inesperados, se deben buscar efectos diferentes más bien que similares, con respecto a drogas conocidas. En el presente trabajo se evaluaron los efectos conductuales de dos benzamidas, la sulpirida y la tiaprida, enfatizando los rasgos que las diferencían de otras drogas. Se emplearon ratas y gatos como sujetos y se mantuvo la ejecución por medio de programas aversivos y de reforzamiento positivo. Las benzamidas

exploradas no se ajustan simplemente a los marcos clasificatorios de la psicofarmacología actual, puesto que varias diferencias fueron evidentes con respecto a los efectos conductuales de compuestos bien conocidos.
       DESCRIPTORES: Farmacología conductual, benzamidas, ratas, gatos.

The development of operant techniques has been contemporary with the development of psychotropic drugs around the middle of our century. This was an exceptionally favourable circumstance to test the potentialities of the experimental analysis of behavior in a new field of applications. The outcome has been rapid and impressive, if we evaluate it by the number and the variety of researches. It has been, no doubt, extremely fruitful if we look at the contribution of behavioral pharmacology to the general field of psychopharmacology. Not only behavioral data from operant conditioning studies stand in good place in the array of preclinical investigations of almost any psychotropic drug; but, more important, concepts derived from the experimental analysis of behavior have become common tools in modern psychopharmacological thinking. Drug-behavior interaction, behavioral toxicity, stimulus properties of CNS drugs, behavioral tolerance, behavioral reference for neurophysiological and neurochemical facts, state dependent learning, are but a few illustrations of such concepts.

Comparing behavioral results with pharmacological data on the one hand and with clinical action of drugs on the other provides for increasingly coherent classifications of psychotropic agents. Such classifications, however, must be considered as provisional, as long as the mechanisms of action are not fully elucidated, and as long as new molecules are proposed for screening. An interesting daily problem in psychopharmacological research is how to characterize the action on behavior of a new compound. At the stage of rapid screening —an inescapable stage in industrial research, given the number of compounds turned over to the pharmacologists by the chemists— the general tendency is to look first for effects similar to those of well-known classes of drugs. The new molecules are assessed against some reference drugs: major tranquilizers, minor tranquilizers, psychostimulants, and so on. The limitations of this purely analogical process have been repeatedly emphasized: it leads to the discovery of equivalent drugs, but gives little chance to discover original different agents. It takes for granted the rationale of present classifications, that should rather be considered as useful working hypotheses.

If we want to detect possible unexpected effects, we must turn to a more refined analysis, using diversified and complex experimental tests, and look for different rather than similar effects, with respect to known drugs. Operant techniques recommend themselves for that kind of descriptive analysis, the results of which might suggest new classes or subclasses of psychotropic drugs, or, more ambitiously, might lead to a revision of accepted classifications. The present paper aims at characterizing the behavioral effects of two benzamides, namely sulpiride and tiapride, by pointing to distinctive featu-

res that differentiate them from other drugs. The chemical formula of each compound is given in Fig. 1.
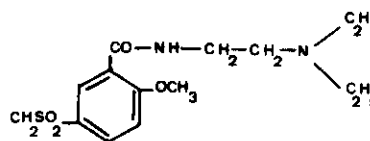
BENZAMIDES

ALKYLSULFONE—O—ANISAMIDES

SULPIRIDE   **TIAPRIDE**
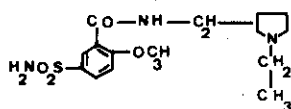
DOGMATIL   **TIAPRIDAL**

Fig. 1. Chemical formulae of sulpiride and tiapride.

Benzamides are recently commercialized substances with psychotropic properties. As with a number of earlier drugs now widely used in clinical practice, the psychotropic properties were recognized through usual pharmacological screening methods and put to clinical tests before a more detailed behavioral analysis was undertaken.

In pharmacological screening tests on animals, sulpiride has been shown to have strong antiemetic action, as is classically observed with neuroleptics (Llaville and Margarit, 1968), but, at normal doses, only a slight cataleptic effect (Takaori, 1969). Its toxicity is very low, with a lethal ED 50 of 210 mg/kg IP in mice (Kumada, 1968). Sulpiride is presented to clinicians as a neuroleptic drug, having in addition, antidepressive and tranquilizer-like effects. It is also used in the treatment of diseases of the gastrointestinal tract primarily of gastroduodenal ulcers (Cornet and Grivaux, 1968). This makes it a drug with a rather wide spectrum.

Tiapride, though chemically close to sulpiride, has little neuroleptic action (as assessed by current pharmacological screening) (Laville and Margarit, 1977). It is used in the treatment of abnormal movements in various neurological diseases, in the treatment of chronic and acute alcoholism, and in various kinds of cephalalgias and muscle pains. Its action on behavioral disturbances, involving agressivity or psychomotor irritability has also been reported.

METHOD

In order to maximize our chances to detect original effects of a drug, it is good experimental strategy to use a number of different situations. Thus a complex profile of action will be determined rather than only the effect on a single kind of behavior.

Two species, rats and cats, have been used. Combination with other drugs have been studied in order to refine further the comparative analysis. All experiments took place in isolated experimental chambers of appropriate size equipped with a response-lever and a food dispenser and/or shock scrambler. One hour sessions were run five days a week (or daily in chronic treatment, not reported here). Drug was administered intraperitoneally 30 min. before the session with no new injection made unless the subject had recovered base-line behavior on the previous day. Exception to that rule had to be made ocassionally when a drug-induced change did not reverse after a few days.

Behavioral effects of sulpiride have been investigated in rats using the following schedules of reinforcement:

Fixed Interval 2 minutes. (FI 2 min): The reinforcement is available after a delay of 2 min. has elapsed since the previous reinforced response; as in all operant situations, the reinforcement is contingent upon the emission of a response.

Differential Reinforcement of Low Rates of Responding. (DRL 30 sec): reinforcement is contingent upon the spacing of responses by 30 sec at least.

Variable Interval with Conditioned Emotional Response. (VI 2 min CER): the reinforcement is available after an unpredictable delay, averaging 2 min, superimposed on these contingencies, a 2 min auditory signal is ocasionally presented, followed by an inescapable electric shock.

Multiple Fixed-Ratio-Extinction. (Mult-FR 26 Ext): Extinction periods of 6 min alternate with 15 min periods where reinforcement is contingent upon the emission of 26 responses; different combined auditory and visual stimuli are associated with each component.

Non-discriminated Sidman Avoidance. (Sid. Av. SS: 5, RS: 20): Each response postpones an impeding shock by a 20-sec delay, otherwise shocks are delivered at 5 sec intervals.

Signalled Avoidance. A 10 sec auditory stimulus is presented randomly and followed by shock, the subject may avoid this shock by pressing the lever in the presence of the stimulus.

In cats, the Fixed-Interval schedule and Mult FR 26 Ext, as defined above, were used. In addition, a schedule of reinforcement of response duration was studied, in which the subject had to keep a lever down for between 10 and 13 sec.

Doses of sulpiride ranged from 1 to 150 mg/kg for rats, from 1 to 40 or 100 mg/kg for cats. Five rats, males or females, were assigned to each schedule, while 3 cats were used under each condition. Tiapride has been administered to rats on the following schedule of reinforcement: Fixed-Interval 2 min, Fixed Ratio 20, Variable-Interval with Conditioned Emotional Response (VI-CER), Sidman Avoidance, Discriminated Avoidance, and to cats on Fixed Ratio 20, Fixed Interval 2 min and Sidman Avoidance. Doses explored ranged from 1 to 20 mg/kg for rats and 0.5 to 20 mg/kg for cats.

Systematic comparisons and associations with other psychotropic drugs were made. Reference drugs were diazepam, meprobamate and thioridazine.

RESULTS

A detailed account of the results would be outside the scope of this paper. Part of the data concerning sulpiride can be found in Fontaine et al. (1974) and Fontaine et al. (1975). We shall only summarize·the main features that characterize behavior under these drugs.

Sulpiride

As a general rule, the effect of sulpiride on rate of responding is a decreasing effect. Figures 2, 3 and 4 illustrate this for three schedules on rats.
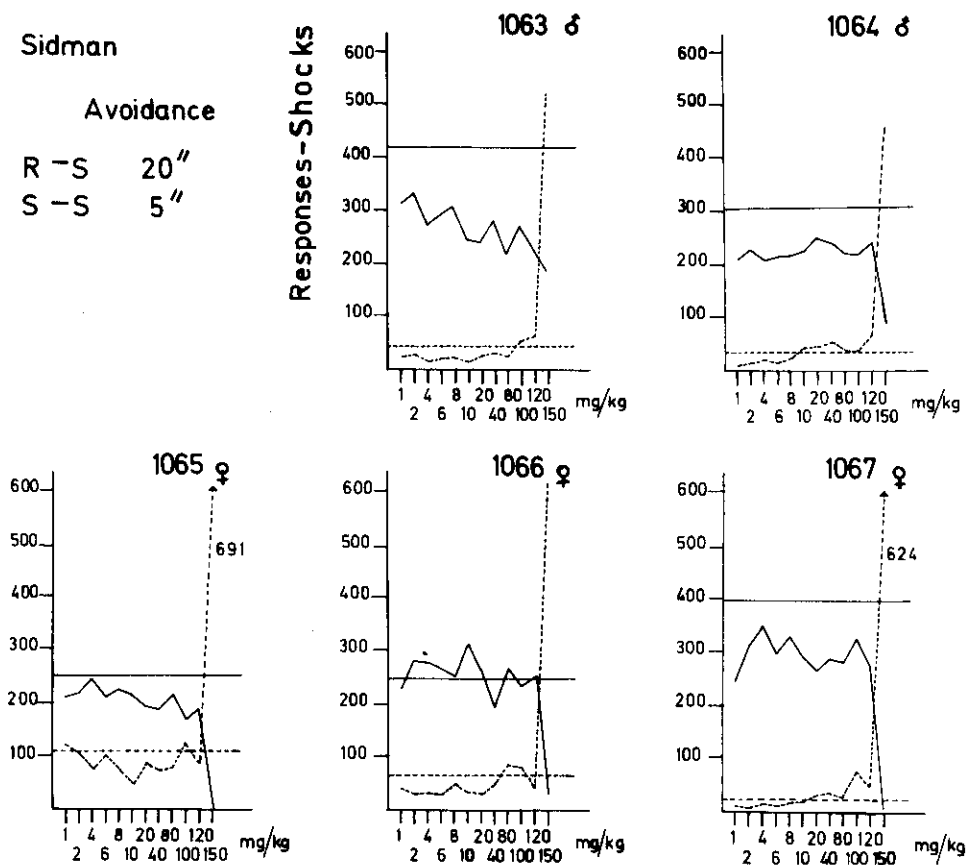

Fig. 2. *Sidman avoidance in Rats.* Response rate per session (1 hour) and number of shocks received (dotted line) as a function of doses of sulpiride. Horizontal lines give the base-line control mean, computed on the last ten sessions before drug administration.
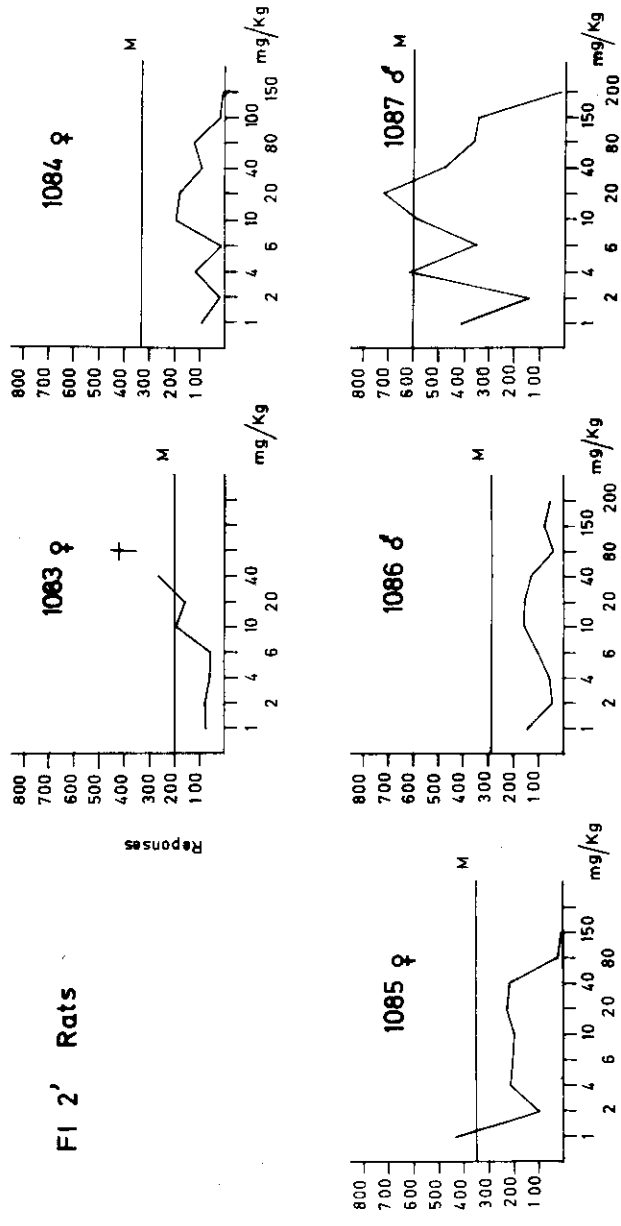
FI 2' Rats

Fig. 3. *Fixed-Interval 2 min in Rats.* Response rate per session (1 hour) as a function of doses of sulpiride. The horizontal line gives the base-line control mean. Rat 1083 died in the course of the experiment.
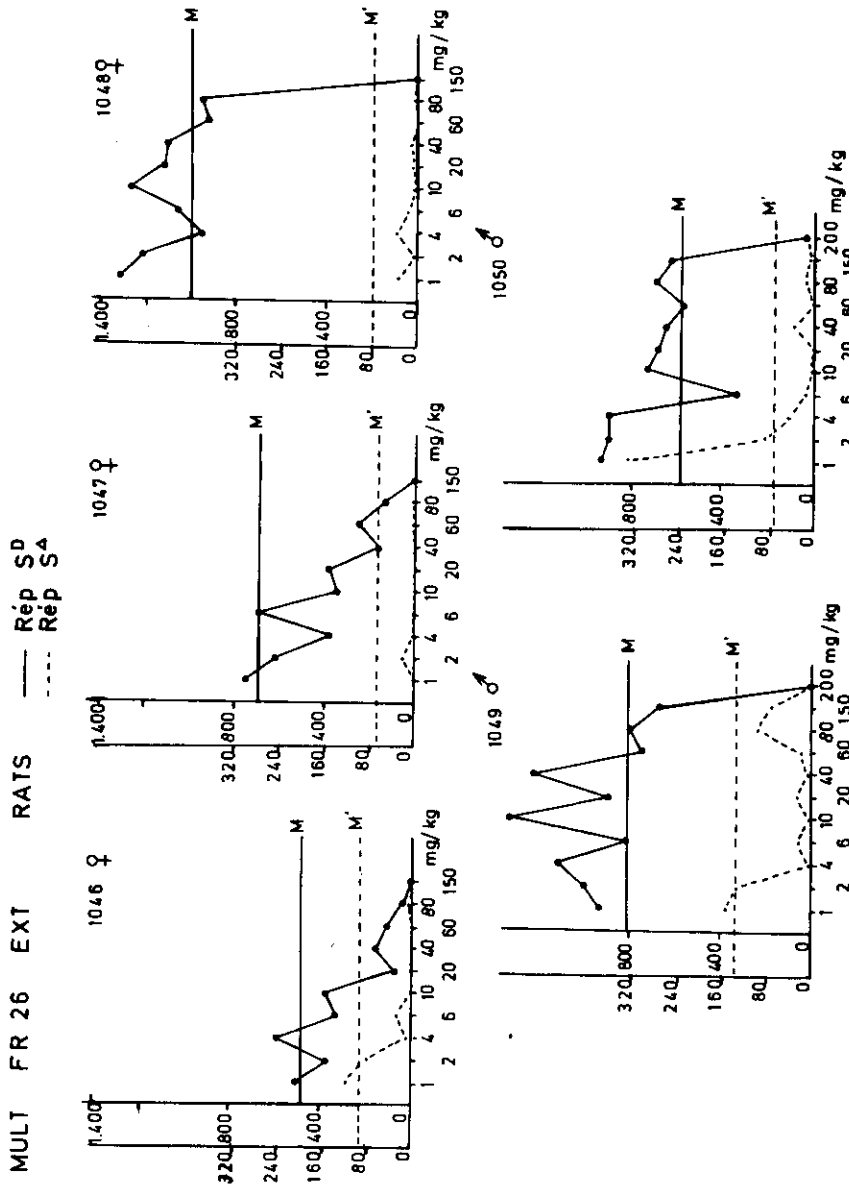
Fig. 4. *Multiple Fixed-Ratio 26 — Extinction in Rats.* Response rate per session (1 hour) as a function of doses of sulpiride. Solid line and right side ordinate axe: responses in the Fixed-Ratio component; dotted line and left side ordinate axe: responses in the Extinction component. Horizontal lines give the baseline control means, computed on the last ten sessions before drug.

Results on other schedules, not shown for reason of space, are similar in that respect. But there are a number of peculiarities that make this general effect quite distinctive.

1. The dose-response curves differ markedly depending upon the contingencies. In rats, for instance, Differential Reinforcement of low rates of responding (DRL) and Sidman Avoidance schedules show much more resistance to the drug effect than Fixed Interval. While the rate is only slightly affected until the dose of 150 mg/kg in non-discriminated Sidman Avoidance, it significantly drops in Fixed Interval schedule at doses as small as 1 or 2 mg/kg (Figs. 2 and 3). This contrast is not one opposing positive and aversive contingencies, since a dose relation similar to that observed in non-discriminated Sidman Avoidance is found in the Fixed Ratio component of the Multiple Fixed-Ratio Extinction (with some subjects presenting no decrease until the dose of 200 mg/kg) (Fig. 4). Dews' hypothesis relating the decreasing or increasing effect on rate to initial rate value is not confirmed: the decreasing effect is much more marked in Fixed Interval, where the baseline value is within the range of 200 to 600 responses per hour (depending upon the individual) than in Fixed-Ratio, where the baseline values range from 500 to 1000 responses.

2. The dose-rate curves in Fixed Interval show a typical pattern: the decreasing effect is pronounced at small doses (1-6 mg/kg) but less marked at intermediate doses (10-40 mg) and reaches a maximum at the largest doses (80 to 200 mg/kg) (Fig. 3). This is an unusual pattern, different from what is found with classical neuroleptics such as phenothiazines and butyrophenones (where a progressive decrease is observed as doses are increased) as well as from what is found with minor tranquilizers (where increasing effects occur, if ever, with smallest doses and give place to decreasing effects at high doses).

3. The dose-effect curves show marked differences depending upon sex. With few exceptions, females exhibit more sensitivity to sulpiride than males. These differential effects might be related to hormonal effects reported in some pharmacological studies and in some clinical observations.

4. Though the concept of adaptation to the contingencies is by no means a simple one, it is not unreasonable to talk about degree of adjustment with some schedules. For example, the efficiency ratio and the Inter Response Time distribution may be said to reflect a good or poor adjustment to Differential Reinforcement of low rates of responding (DRL) contingencies. Similarly, the percentage of shocks avoided and the response/shock ratio in Sidman Avoidance, or the number of responses in the Extinction component of a multiple schedule may be considered as indicators of adaptation to the contingencies. These indicators can be affected indirectly by a drug. For instance, more reinforced responses may result from a decrease in rate in DRL responding whereas fewer shocks received may be a consequence of an increase in rate in Sidman Avoidance. In such cases, better adjustment is merely a by-product of some other primary effect. However, when discriminative behavior, temporal regulation, or avoidance are improved after drug

administration in a way that cannot be accounted for by some non specific effect, it is legitimate to talk of *regulatory effect* (of course always relative to the contingencies). Such effects are observed with sulpiride in Sidman Avoidance, in Signalled Avoidance, in Multiple-Fixed-Ratio-Extinction and in Differential Reinforcement of low rates of responding schedules. Typically, the number of shocks in Sidman Avoidance is decreased though the number of responses is unchanged or, if anything, decreased. This can be seen from results summarized in Fig. 2, and is illustrated by the cumulative curves of an individual subject in Fig. 5.
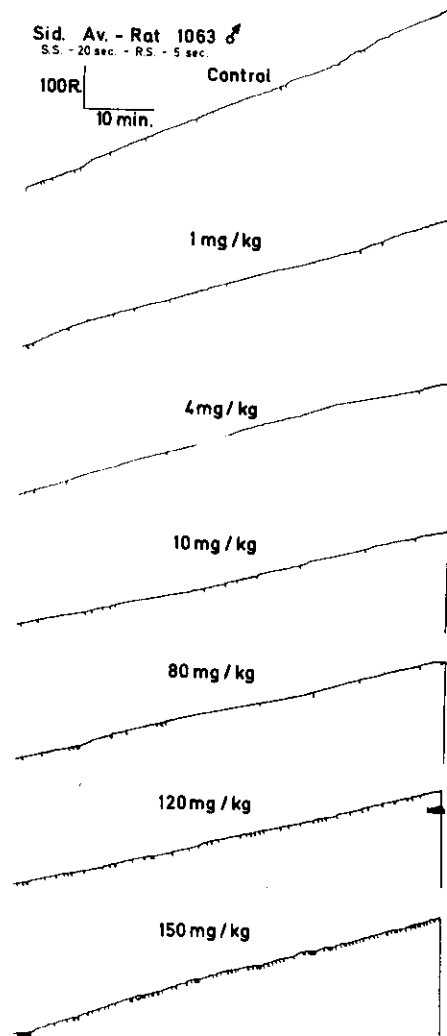

Fig. 5. Cumulative curves in Sidman avoidance schedule for one individual rat, under increasing doses of sulpiride. Note the very few shocks received under 1 mg and 4 mg/kg though the response rate is reduced.

Subjects who perform poorly in the signalled avoidance schedule drastically improve after small doses of the drug. Figure 6 shows the results for the five rats in this group. Two of them have a near hundred percent avoidance score prior to the drug administration. The others have a score largely inferior, and produce significantly more avoidance responses under drug.
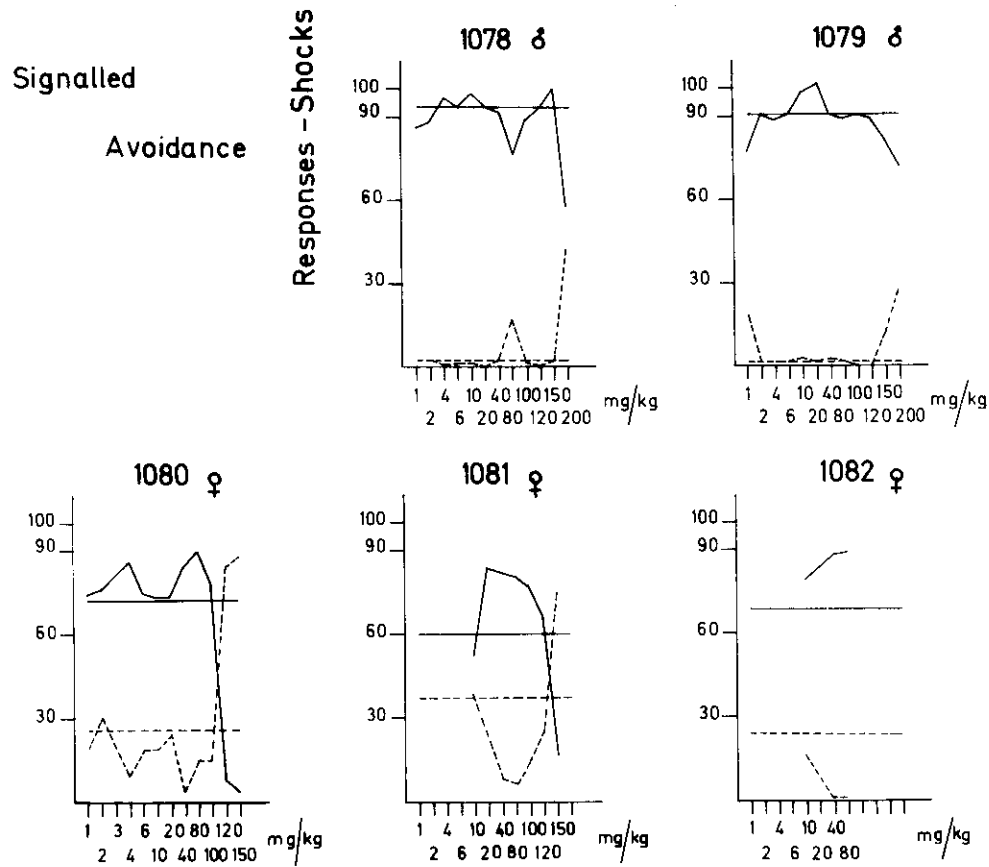

Fig. 6. *Signalled avoidance in Rats.* Percent of avoidance responses relative to the number of occasions to emit avoidance responses (i.e. number of signals) (solid line) and percent of shocks received (dotted line) as a function of doses of sulpiride. Rat number 1082 died after the dose of 40 mg/kg from a disease unrelated with the drug injection.

The Inter-Response Times distribution in Differential Reinforcement of low rates of responding is shifted toward the reinforced value. Figure 7 illustrates this effect in two subjects.

The number of responses emitted during the Extinction phase of the Multiple Fixed Ratio-Extinction schedule is decreased even when the response in the Fixed Ratio component remains unchanged (see Fig. 4).
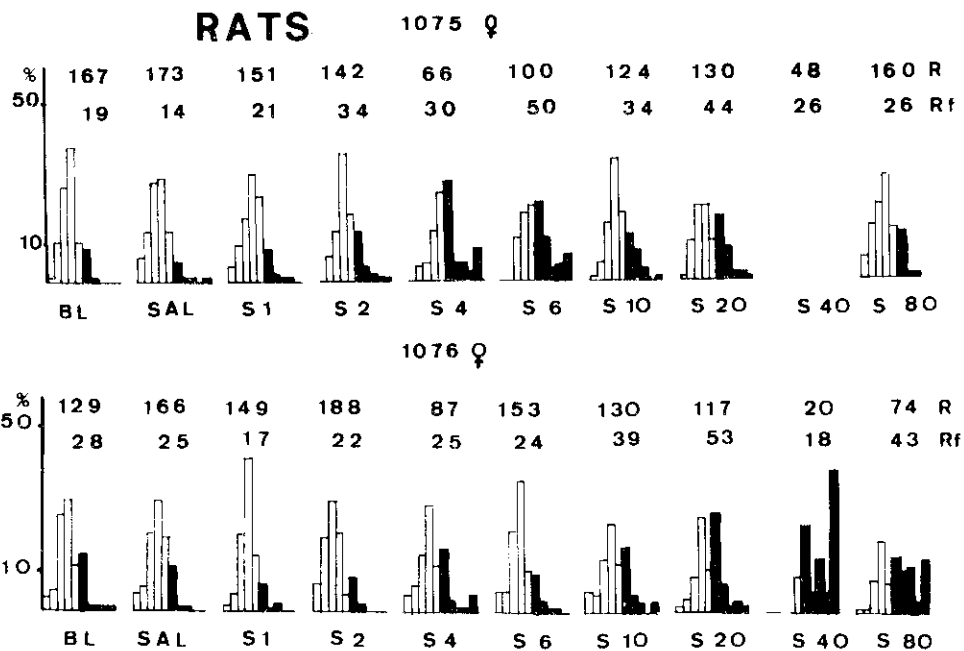
RATS 1075 ♀

Fig. 7. Inter-Response times distributions for two individual rats under the schedule of Differential Reinforcement of Low Rates 30 sec. Abscissa: IRT's in 6 sec classes. Ordinate: relative frequency. Successive histograms from left to right are for averaged control sessions (BL), for control session with saline injection (SAL) and for increasing doses of sulpiride (S) (in mg/kg). Figures above the histograms indicate the absolute number of responses, and the number of reinforcements. Apparatus failure for the session with 40 mg/kg on rat 1075 is responsible for the absence of IRT's.

5. Without going into details of the associations study, it can be noted that sulpiride acts synergically with haloperidol, a member of the class of major tranquilizers or neuroleptics. It does not affect the behavioral effects of diazepam, nor of amitriptyline under the conditions of the present study.

Tiapride

1. When behavioral effects of tiapride are observed, they generally consist of decrease in response rate. Rare individual exceptions concern some cats (not all) under the Fixed Interval 2 min schedule, who show an increase. Typical illustrations of the general effect are given in Figs. 8, 9, 11, 12, 13.

2. This effect, however, in the range of doses explored, is not equally clearcut in all schedules. On the whole, in rats, positively reinforced behavior is slightly altered, if at all, except for the highest doses (15 or 20 mg/kg) (see Fig. 8). The decrease in rate is more pronounced in Avoidance schedule, where a dose-related curve is more commonly obtained (though some individual exceptions are found). An interesting feature contrasting with what we have called a regulatory effect in sulpiride is the increase of the number of shocks, while the number of responses remains unchanged (Figs. 9 and 10).
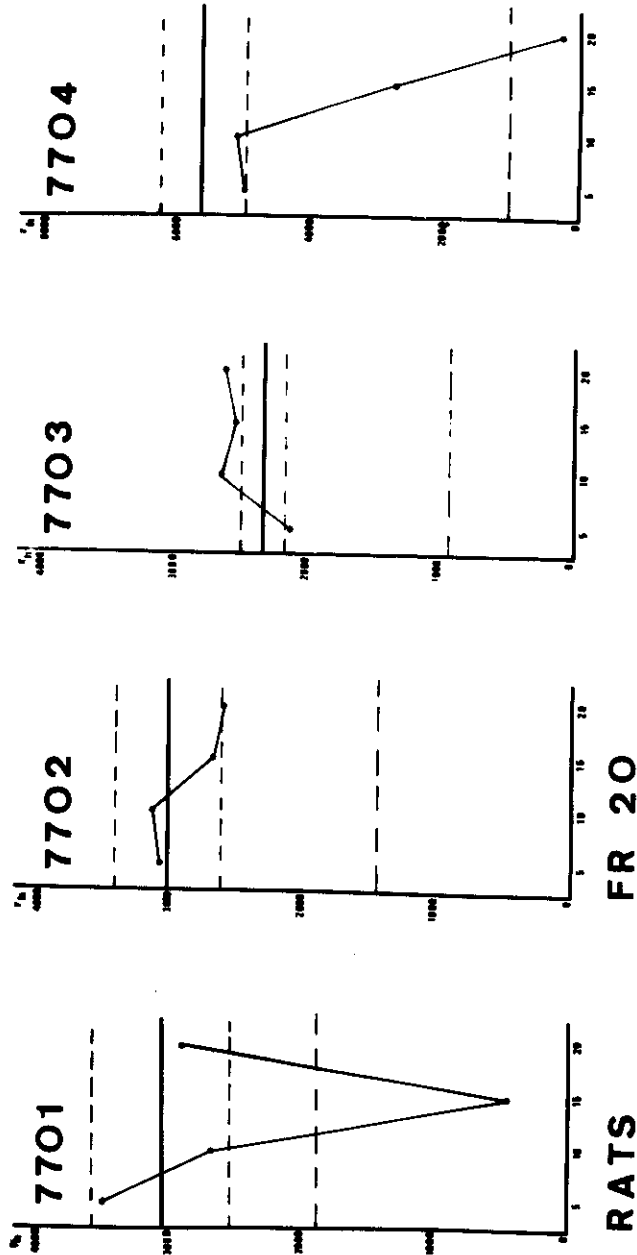
Fig. 8. Response rate per session (1 hour) under Fixed-Ratio 20 in four individual rats, as a function of increasing doses of tiapride in mg/kg of body weight (abscissa). Horizontal lines give the baseline value, averaged from the last ten sessions before drug, and one standard deviation above and below the mean (short interrupted trait). The long interrupted trait may be ignored in the present context.
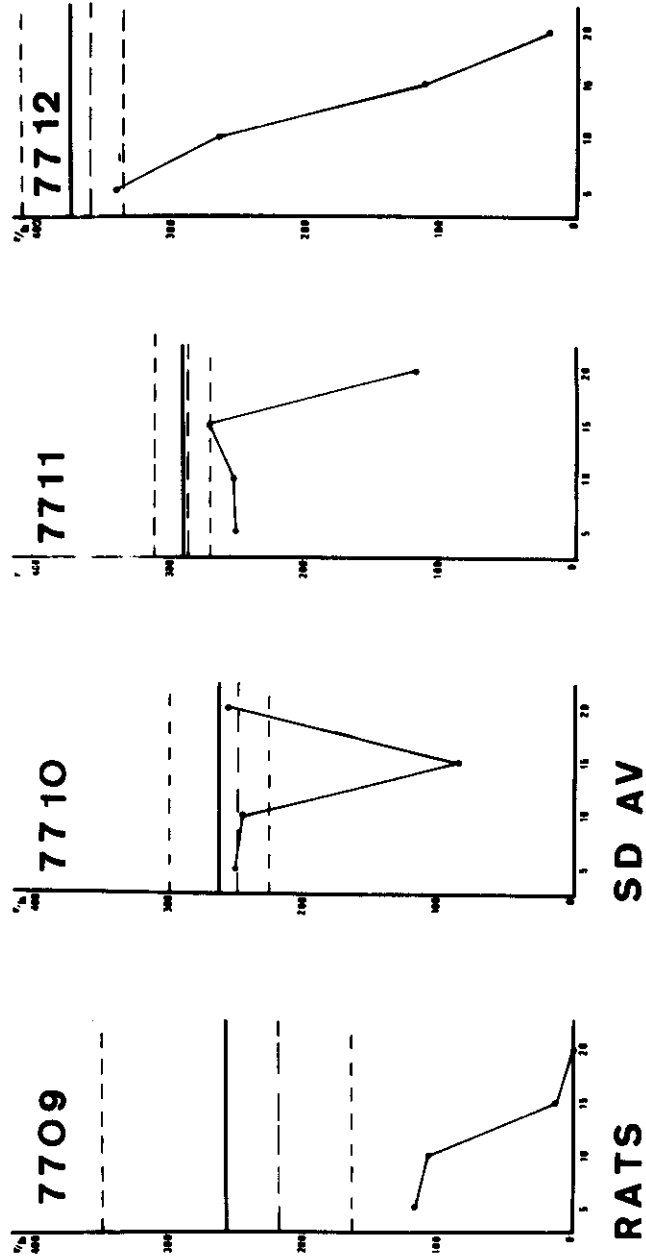
Fig. 9. Response rate per session (1 hour) under Sidman avoidance schedule in four individual rats, as a function of increasing doses of tiapride. See Figure 8 for key to reading.
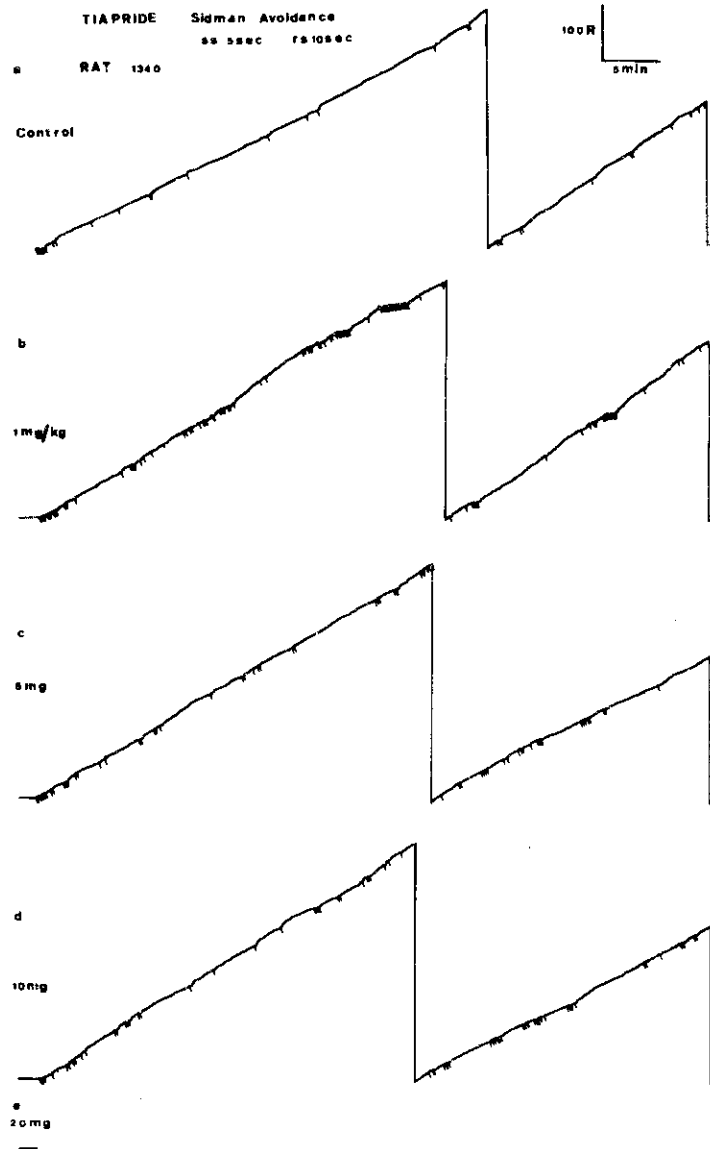
Fig. 10. Cumulative curves in Sidman avoidance for one rat under tiapride. Note the increased number of shocks despite an unchanged rate of responding, compared with the control curve, for the lowest doses (see Figure 5 for comparison with sulpiride).

3. In cats, the decrease in rate is observed more regularly in all three schedules (Fixed Ratio, Fixed Interval, Sidman Avoidance). It also appears more progressively as the dose is increased and finally, it occurs at much smaller doses than in rats. Figs. 11, 12 and 13 summarize results for Fixed Ratio, Fixed Interval and Sidman Avoidance respectively.
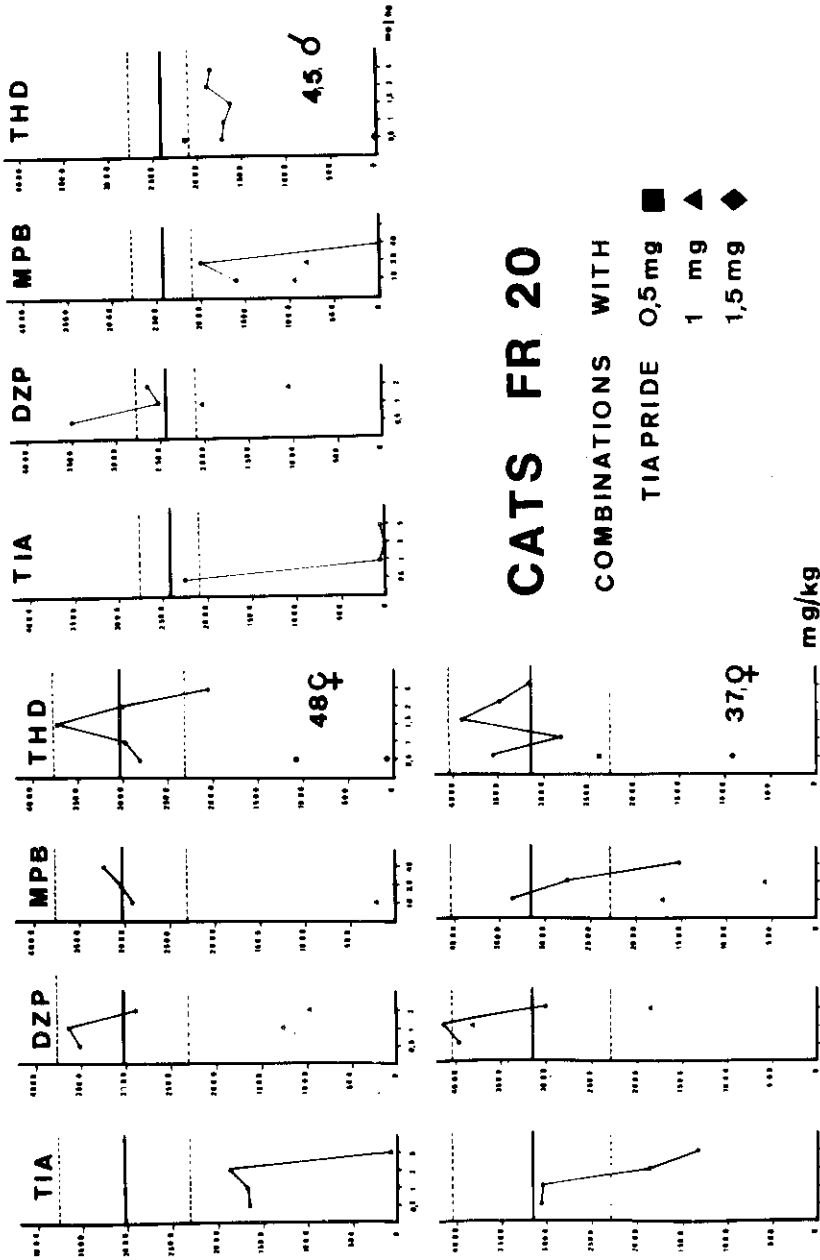
Fig. 11. Response rate per session (1 hr) under Fixed-Ratio 20 in three individual cats as a function of increasing doses of tiapride (TIA), diazepam (DZP), meprobamate (MPB), thioridazine (THD). Points joined by solid lines are for session with these drugs administered alone. Other points are for associations with tiapride, at doses indicated by the symbols in the figure. Horizontal solid lines give the baseline mean; horizontal dotted lines one standard deviation below and above the mean.
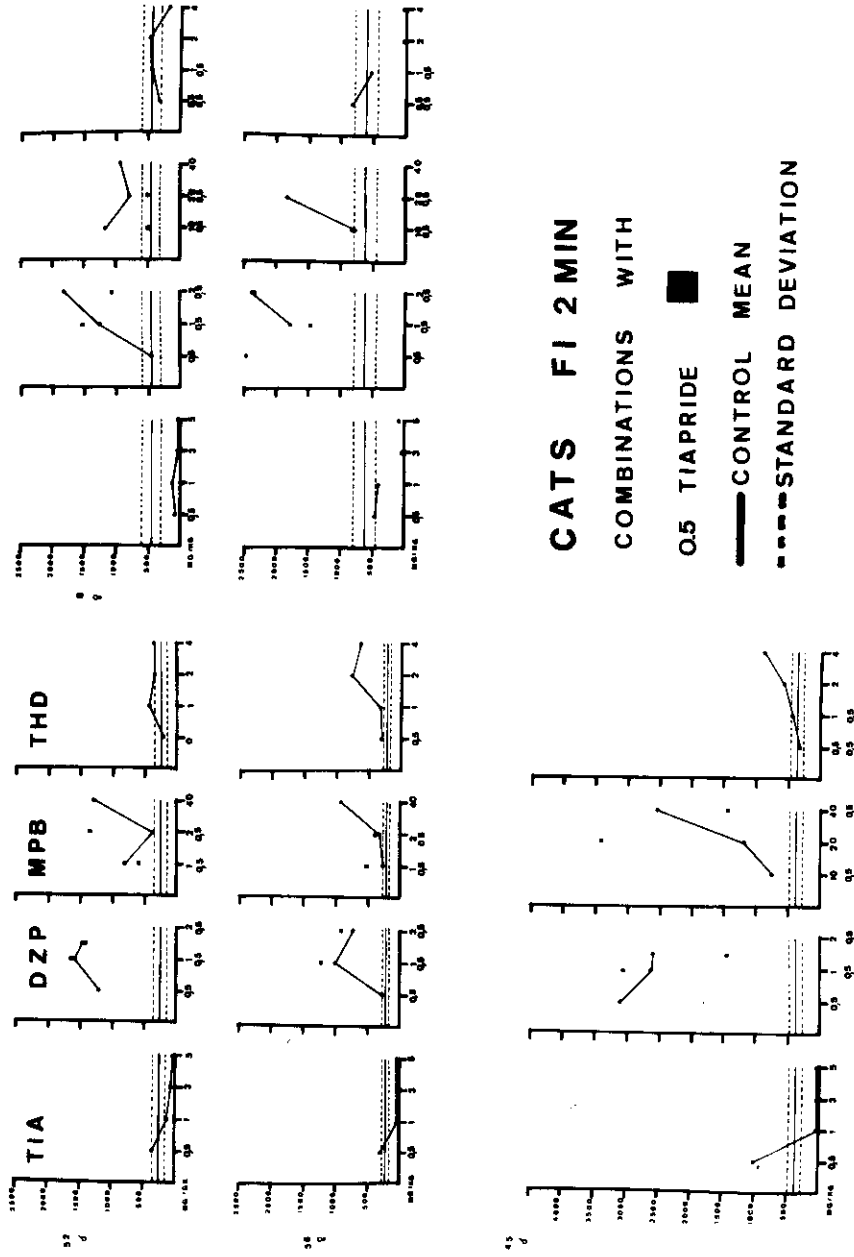
Fig. 12. Response rate per session (1 hr) under Fixed-Interval 2 min in five individual cats as a function of increasing doses of tiapride, diazepam, meprobamate and thioridazine. See Figure 11 for key to reading.
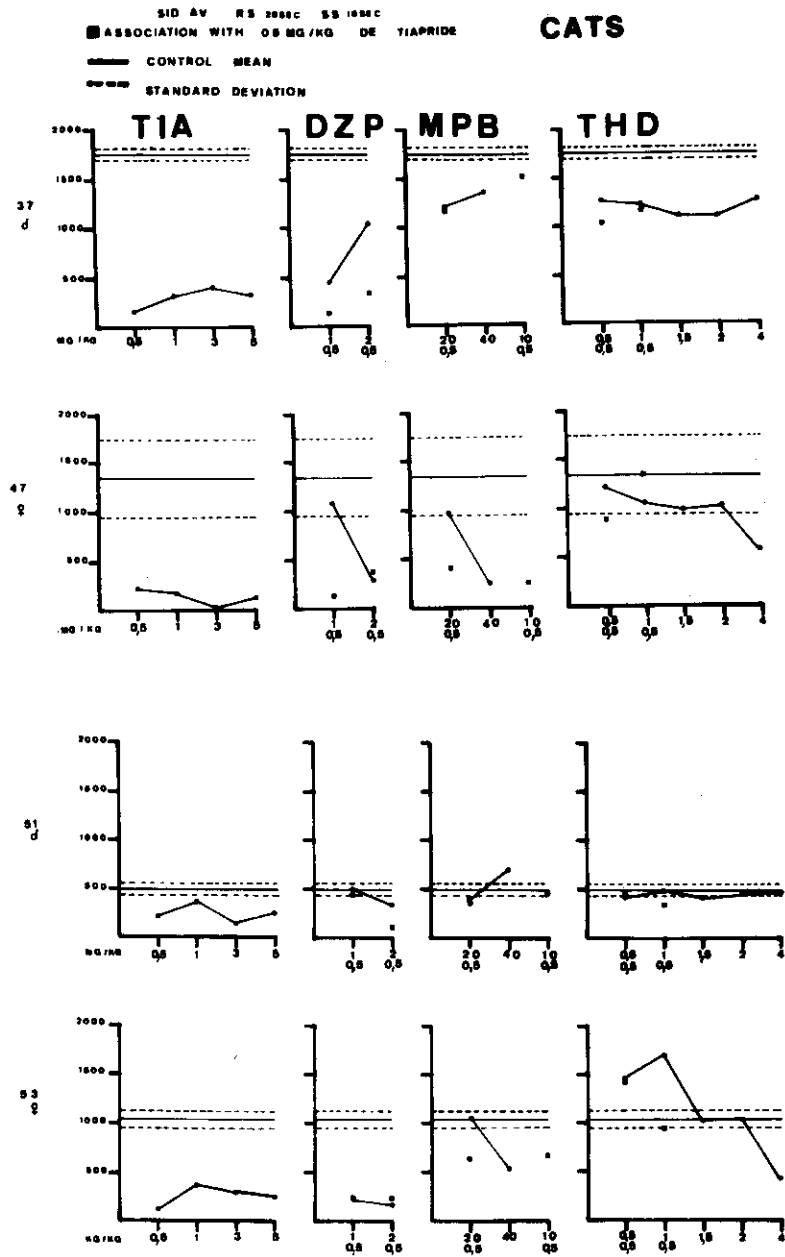
Fig. 13. Response rate per session (1 hr) under Sidman avoidance in four individual cats as a function of increasing doses of tiapride, diazepam, meprobamate and thioridazine. See Figure 11 for key to reading.

4. Comparisons with other drugs indicate that tiapride does not act strictly as do the minor tranquilizers, diazepam and meprobamate. The decreased rate effect normally observed with the latter in rats is more clearly dose-related, and it is more pronounced in positively reinforced behavior than it is with tiapride. Conversely, avoidance behavior shows more resistance to meprobamate and diazepam than to tiapride. Contrast is obvious in cats: minor tranquilizers affect little Fixed Ratio behavior (despite initial high rates), they reduce rate in Sidman Avoidance (what tiapride does too), but they increase rate drastically in Fixed Interval (while tiapride reduces it).

The action of tiapride is closer to that of thioridazine, though the benzamide is more active than the phenothiazine derivative at doses used.

5. Associations with these drugs present a complex picture that cannot be canalyzed in detail here. The general trend is synergic action, that can be expected when each of the combined drugs produces a similar effect when administered alone. Examples from cats can be found through inspection of Figs. 11, 12 and 13.

Puzzling results however are obtained under Sidman Avoidance in cats (and occasionally under other contingencies in cats and rats as well): while all drugs including tiapride depress rate of responding and increase the number of shocks in Sidman Avoidance, some associations produce a less pronounced decrease than tiapride alone. This is especially the case for thioridazine, as shown in Fig. 13. This can be interpreted as an antagonistic effect, where the associated drug neutralized to some extent the effect of tiapride. Antagonistic effects where tiapride, though acting in the same direction as the associated drug when administered alone, neutralized or reverses the effects of the associated drug are also observed. An example can be found in Fixed Ratio schedule for Rat.

Finally, simple antagonism is observed when both drugs act in opposite direction, as in the case in associations of tiapride with diazepam or meprobamate in cats under Fixed Interval (see Fig. 12).

DISCUSSION

The two benzamides, sulpiride, exhibit behavioral effects on operant conditioned responses. Though the general trend for both drugs is a depressing effect on rate of responding, the fine analysis of results in various contingencies does not allow us to classify them simply among neuroleptics or major tranquilizers. One main difference is the contrasting resistance of learned behavior in some schedules (especially positively reinforced schedules) as compared with the sensitivity observed under other contingencies. Another difference is the irregular dose-response curve: in some cases, the transition from ineffective to effective dose is abrupt, in other cases the dose-effect curve is not linear. In addition, sulpiride presents regulatory effects not described with phenothiazine or butyrophenones.

Sulpiride and tiapride are neither quite similar to diazepam or meprobamate, though in several schedules they do show similar depressing effects on rate. They clearly differ in cats under Fixed Interval schedules, where diazepam and meprobamate are known to increase rate drastically. They also produce no tolerance, while meprobamate and chlordiazepoxide do.

The study of associations also confirms the distinction outlined here. For instance, it is striking that combining two clearly depressing doses of tiapride and of thioridazine may result in normal-like rate.

Detailed analyses also show that sulpiride and tiapride differ from each other as far as behavioral effects are concerned. If we consider the rate-decreasing effect as a primary feature of behavioral action of neuroleptics, sulpiride is closer to the normal pattern than tiapride. This may be only a matter of degree. More important, though more subtle, might be the absence of regulatory effect in tiapride.

These benzamides do no fit simply into the classificatory frames of our present psychopharmacology. The data from experimental studies converge with those of clinical observation to evidence a wider spectrum on the one hand, and less clearcut types of actions on the other. Should we change our usual criteria for defining neuroleptics, so that we could feel authorized to include sulpiride in this class (what we shall do with tiapride is another question, as it is not a neuroleptic by the usual pharmacological criteria)? Should we build new classes for our new drugs? Or should we get rid of classes for a while, and look at the great varieties of effects observed on animal behavior without now attempting to reduce them to order? We favor the latter, complemented by a parallel unbiased analysis of clinical effects. At both levels, premature classification may be unwarranted in this as yet adolescent science.

REFERENCES

Cornet, A. and Grivaux, M. Recherche physiopathologiques sur le sulpiride en gastroentérologie. *Bull Soc. méd. Hop. Paris,* 1968, *119,* 753-760.

Frontaine, O., Hauglustaine, A., Libon, P. and Richelle, M. Action du sulpiride sur le comportement operante chez l'animal. *Thérapie,* 1975, *30,* 573-584.

Fontaine, O., Libon, P. and Richelle, M. Action of a new psychotropic drug (sulpiride) on avoidance behavior in rats. *Psychopharmacologia,* 1974, *39,* 309-314.

Kumada, S. The circumstances of discovery, general pharmacological finding and virulence of dogmatil (sulpiride). *Vth Congress Ther. Res. in New Drugs, Tokyo, Rep. Val.,* 1968, 21-27.

Laville, C. and Margarit, J. Activité antiémétique du sulpiride vis-à-vis des divers poisons émélisants chez les chiens. *Compte-Rendus Société Biologie* (Paris), 1968, *162,* 869-874.

Laville, C. and Margarit, J. Propriétés pharmacologiques du tiapride. *Sem. Hôp. Paris,* 1977, *53,* 77-83.

Takaori, S. Central action of sulpiride. *Vth Congress Ther. Res. in New Drugs, Tokyo,* Rep. Vol., 1968, 35-47.