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Specificity of the Learned Helplessness Model of Depression

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SHERMAN, A D, J L SACQUINTNE AND F PETTY *Specificity of the learned helplessness model of depression* PHARMAC BIOCHEM BEHAV **16**(3) 449–454, 1982 —The learned helplessness model of depression was tested for its responsiveness to several types of antidepressant therapies, and to a number of psychoactive drugs which are not effective in treating depression in humans Chronic administration of tricyclic antidepressants (imipramine, desipramine, amitryptyline, nortryptyline, or doxepin), atypical antidepressants (iprindole or mianserin), monoamine oxidase inhibitors (iproniazid or pargyline), or electroconvulsive shock was effective in reversing learned helplessness Chronic treatment with anxiolytics (diazepam, lorazepam, or chlordiazepoxide), neuroleptics (chlorpromazine or haloperidol) stimulants (amphetamine or caffeine), or depressants (phenobarbital or ethanol) was not Thus, this model provides a reasonable degree of specificity toward therapies which are successful in humans

Learned helplessness Antidepressants Depression

ONE of the major difficulties in attempting to define the mechanism of action of antidepressants lies in the status of the various animal models of depression Several [4,11] appear promising, but have not been subjected to rigorous pharmacological testing due to the nature of the models Another [9,10] has been shown to have significant promise, but requires only acute administration of drugs, while a delayed onset of action is characteristic of antidepressants used clinically

The learned helplessness model [7,12] has also been demonstrated to be a useful one The model involves exposure of animals to inescapable shock and observing the subsequent retardation of the acquisition of tasks reinforced by appetitive or aversive reinforcers

The reversal of learned helplessness (i e , restoring normal responding) can be achieved by chronic administration of desipramine [6] or imipramine [8], or by acute administration of anti-vasopressin serum intraventricularly [5], or with apomorphine or clonidine [3] or DOPA The acutely-derived effects are generally observed only with particular escape tasks are employed

The purpose of the present study was to determine whether the learned helplessness model demonstrated drug specificity similar to that described for the "behavioral despair" model of Porsolt [9,10] The behavioral despair model has been demonstrated to be responsive to acute administration of a number of tricyclic antidepressants, atypical antidepressants, and monoamine oxidase inhibitors These drugs all alter the onset of immobility but do not increase locomotor activity as measured in an open-field maze Stimulants also alter the onset of immobility in a manner similar to antidepressants, but also increase locomotor activity, and thus can be differentiated from antidepressants The onset of immobility in this test is also altered by several non-pharmacological treatments including convulsive shock, deprivation of REM sleep, and an enriched environment, while these measures do not increase open-field locomotor activity

METHOD

Male Sprague-Dawley rats (200–250 g) were group-housed with free access to food and water during all phases of the study They were maintained on a 12 hour light-dark cycle, with lights on from 0600–1800 All injections, training, and testing took place between 0700 and 1100 daily

All animals were exposed to learned helplessness training on day 1 [13] This consisted of a single 40 minute training session Random shock (0 7 mA) was delivered through the grid floor of a Coulbourn test cage The onset and offset of the shock were established through a random probability generator which resulted in the shock being on half the time This random shock schedule insured that both shock onset and shock termination were independent of the ongoing behavior over the course of 40 minutes, but results in a different shock schedule being presented to each animal

After training, animals were injected intraperitoneally with one of the doses of drug, and injections were repeated once daily on days 2, 3, and 4 All drugs were administered as the water-soluble salt in saline, and doses were calculated as the free base Animals receiving electroconvulsive shock were treated twice daily, (beginning on the afternoon of day

TABLE 1
AVERAGE LATENCY IN BLOCKS OF THREE TRIALS

Condition	Block 1	2	3	4	5
Naive Controls	34 ± 27	19 ± 13	10 ± 8	6 ± 5	5 ± 5
Saline	35 ± 20	16 ± 11	9 ± 6	7 ± 4	4 ± 5
Desipramine (10)	41 ± 17	22 ± 10	11 ± 7	8 ± 5	7 ± 4
Imipramine (10)	37 ± 12	15 ± 8	12 ± 6	9 ± 4	5 ± 3
Amitriptylene (10)	40 ± 13	21 ± 9	16 ± 11	8 ± 5	7 ± 4
Nortriptylene (10)	37 ± 14	19 ± 11	9 ± 7	9 ± 6	7 ± 4
Doxepin (10)	39 ± 18	17 ± 9	9 ± 6	7 ± 5	6 ± 4
Iprindole (10)	36 ± 14	21 ± 12	11 ± 8	6 ± 5	7 ± 4
Mianserin (10)	44 ± 19	19 ± 11	11 ± 7	4 ± 6	5 ± 4
Iproniazid (20)	38 ± 16	18 ± 10	9 ± 5	10 ± 7	4 ± 5
Nialamide (20)	40 ± 18	20 ± 11	11 ± 6	8 ± 7	7 ± 6
Diazepam (3)	39 ± 17	20 ± 10	12 ± 9	5 ± 6	7 ± 4
Lorazepam (1)	40 ± 10	19 ± 8	9 ± 7	7 ± 5	7 ± 6
Chlordiazepoxide (10)	42 ± 18	17 ± 7	11 ± 4	9 ± 6	8 ± 4
Chlorpromazine (10)	39 ± 14	20 ± 10	10 ± 6	9 ± 6	4 ± 4
Haloperidol (4)	42 ± 19	14 ± 10	14 ± 6	11 ± 4	3 ± 6
Amphetamine (3)	40 ± 17	21 ± 9	9 ± 7	6 ± 4	6 ± 5
Caffeine (10)	37 ± 10	19 ± 7	9 ± 6	9 ± 7	7 ± 4
Phenobarbital (15)	44 ± 18	26 ± 10	12 ± 9	8 ± 6	9 ± 6
Ethanol (1000)	42 ± 18	19 ± 10	13 ± 8	8 ± 6	5 ± 5
ECS	44 ± 18	21 ± 9	13 ± 4	7 ± 6	8 ± 4

Data represent mean ± S D latency (seconds) for blocks of three trials Dose of drug is mg/kg in parentheses Animals received drug for four days before testing

1) for the same amount of time Convulsive shock was administered at 100 mA for 0 25 seconds through ear-clip electrodes All animals receiving this treatment sustained maximal clonic-tonic seizures of at least 10 seconds duration Controls received either intraperitoneal saline injections daily, or received sub-convulsive electric shock through ear-clip electrodes Sub-convulsive shock was administered at 40 mA for 0 25 seconds No animal in this group was observed to demonstrate a seizure within 5 minutes of shock All drugs were either obtained commercially, or were gifts from the manufacturer On day 5, animals were injected with drug (or saline) one hour before testing for the escape deficit characteristic of helplessness The groups receiving electroconvulsive shock and their controls receiving sub-convulsive shock were not treated on day 5

Testing was carried out in a Coulbourn test chamber with a lever mounted 1 cm off the floor on one wall A yellow cue light was mounted 5 cm over the lever A trial was initiated by the onset of a pulsed shock (0 8 mA) which cycled on for 40 msec and off for 360 msec and was terminated either by a lever press or the passage of 100 seconds without a lever press The yellow cue light was activated with each shock cycle A 24 second intertrial interval followed each trial, and 15 trials were given

Response latencies were determined to the nearest second on each trial Based on previous naive control populations, a response within 20 seconds of shock onset was defined as a successful escape, while responses with greater latencies were defined as failures to escape Using this criterion (i e , latency of less than 20 seconds) 607 of 623 controls (97%) completed the 15 trials with five or fewer escape failures, thus defining normal limits for acquisition of this escape task

To establish whether any of the drugs had a direct effect on acquisition of the escape task used to evaluate whether animals were helpless or not, the highest dose of each of the drugs was administered for four days to naive controls which were tested in the escape task on day 5 without receiving any other treatment

RESULTS

Drug effects on acquisition of the escape response were minimal None affected the average latency on blocks of three trials (Table 1), the total number of escape failures (Table 2) or the number of animals defined as helpless using the criterion of five or fewer escape failures within 15 trials (Table 3)

The antidepressants, including tricyclics, atypicals, and MAO inhibitors, had variable effects on reversing learned helplessness depending on the measure used Using average latency on blocks of three trials (Table 4), the antidepressants produced consistently decreased latencies (compared to helpless controls) only in the final two blocks, with other differences scattered throughout blocks 2 and 3 Among the non-antidepressants (Table 5), decreased latencies relative to helpless controls were observed with diazepam (3 mg/kg, block 5), lorazepam (block 5), chlordiazepoxide (block 4), haloperidol (block 5,) phenobarbital (block 5) and ethanol (block 4)

TABLE 2

ESCAPE FAILURES FOR 15 TRIALS

Condition	Escape Failures
Naive Controls	3 ± 1
Saline	4 ± 2
Desipramine (10)	3 ± 2
Imipramine (10)	3 ± 2
Amitriptylene (10)	3 ± 2
Nortriptylene (10)	4 ± 3
Doxepin (10)	3 ± 2
Iprindole (10)	3 ± 2
Mianserin (10)	3 ± 2
Iproniazid (20)	3 ± 2
Nialamide (20)	4 ± 2
Diazepam (3)	4 ± 2
Lorazepam (1)	3 ± 2
Chlordiazepoxide (10)	3 ± 2
Chlorpromazine (10)	3 ± 3
Haloperidol (4)	3 ± 2
Amphetamine (3)	4 ± 2
Caffeine (10)	4 ± 2
Phenobarbital (15)	4 ± 1
Ethanol (1000)	3 ± 2
ECS	3 ± 2
Sham ECS	3 ± 2

Data represent mean ± S D escape failures in 15 trials Animals received drugs for four days before testing

TABLE 3

NAIVE ANIMALS REACHING CRITERION FOR HELPLESSNESS

Condition	Helpless/Total
Naive	0/24
Saline	0/12
Desipramine (10)	0/8
Imipramine (10)	0/10
Amitriptylene (10)	0/8
Nortriptylene (10)	0/8
Doxepin (10)	0/8
Iprindole (10)	0/8
Mianserin (10)	0/8
Iproniazid (20)	0/8
Nialamide (20)	0/8
Diazepam (3)	0/8
Lorazepam (1)	0/8
Chlordiazepoxide (10)	0/8
Chlorpromazine (10)	0/8
Haloperidol (4)	0/8
Amphetamine (3)	0/8
Caffeine (10)	0/8
Phenobarbital (15)	0/8
Ethanol (1000)	0/8

Data represent the number of drug-treated animals with six or more escape failures on 15 trials/total number of animals per group

TABLE 4

AVERAGE LATENCY IN HELPLESS ANIMALS—ANTIDEPRESSANTS

Condition	Block of 3 Trials 1	2	3	4	5
Naive Controls	34 ± 27	19 ± 13	10 ± 8	6 ± 5	5 ± 5
Helpless controls	39 ± 16	32 ± 11	20 ± 11	22 ± 7	18 ± 7
Imipramine (5)	37 ± 20	17 ± 16*	9 ± 7*	8 ± 6*	7 ± 6*
Imipramine (10)	42 ± 21	20 ± 17	9 ± 9*	9 ± 11*	8 ± 9*
Desipramine (5)	40 ± 17	24 ± 13	7 ± 10*	6 ± 4*	5 ± 4*
Desipramine (15)	30 ± 21	26 ± 19	14 ± 9	8 ± 6*	7 ± 5*
Desipramine (10)	32 ± 19	13 ± 14*	16 ± 4	9 ± 5*	8 ± 6*
Amitriptylene (5)	34 ± 17	22 ± 11	13 ± 6	8 ± 4*	7 ± 9*
Amitriptylene (10)	29 ± 23	20 ± 13	12 ± 7	10 ± 5*	9 ± 6*
Nortriptylene (10)	33 ± 14	16 ± 11*	13 ± 10	9 ± 7*	9 ± 5*
Doxepin (10)	37 ± 19	24 ± 12	9 ± 13	7 ± 9*	13 ± 11
Iprindole (10)	35 ± 13	12 ± 7*	9 ± 5*	2 ± 4*	5 ± 3*
Iprindole (15)	42 ± 10	16 ± 9	11 ± 6	8 ± 3*	6 ± 4*
Mianserin (5)	36 ± 11	21 ± 9	11 ± 4*	10 ± 4*	9 ± 6*
Mianserin (10)	44 ± 20	16 ± 9*	10 ± 7*	8 ± 4*	8 ± 4*
Iproniazid (10)	39 ± 16	27 ± 14	19 ± 13	15 ± 11	13 ± 12
Iproniazid (20)	42 ± 13	14 ± 9*	13 ± 7	5 ± 3*	4 ± 4*
Nialamide (20)	39 ± 14	22 ± 9	10 ± 6*	7 ± 4*	7 ± 5*
ECS	37 ± 21	19 ± 7*	10 ± 8	4 ± 5*	4 ± 6*

Data represent mean ± S D latency (seconds) in helpless animals treated with antidepressants for four days

*Lower than helpless controls, $p<0.05$ by Randomization test

TABLE 5

AVERAGE LATENCY IN HELPLESS ANIMALS—NON-ANTIDEPRESSANTS

Condition	Block of 3 Trials 1	2	3	4	5
Naive Controls	34 ± 27	19 ± 13	10 ± 8	6 ± 5	5 ± 5
Saline	39 ± 16	32 ± 11	20 ± 11	22 ± 7	18 ± 7
Diazepam (1)	41 ± 15	37 ± 13	23 ± 9	19 ± 11	16 ± 8
Diazepam (3)	37 ± 14	29 ± 11	19 ± 11	22 ± 10	9 ± 7*
Lorazepam (1)	40 ± 16	39 ± 11	20 ± 9	20 ± 11	10 ± 7*
Chlordiazepoxide (5)	43 ± 15	44 ± 12	20 ± 10	11 ± 9*	13 ± 8
Chlordiazopoxide (10)	32 ± 15	30 ± 14	25 ± 12	15 ± 8	12 ± 7
Haloperidol (2)	37 ± 10	32 ± 10	19 ± 13	18 ± 9	9 ± 6*
Haloperidol (4)	39 ± 11	31 ± 11	24 ± 12	16 ± 7	15 ± 6
Amphetamine (0 5)	44 ± 19	32 ± 10	27 ± 10	17 ± 6	16 ± 6
Amphetamine (3)	38 ± 15	42 ± 19	24 ± 9	19 ± 6	13 ± 7
Caffeine (10)	31 ± 9	27 ± 10	24 ± 7	21 ± 13	16 ± 7
Phenobarbital (15)	32 ± 9	34 ± 8	22 ± 9	18 ± 12	10 ± 4*
Ethanol (1000)	37 ± 12	29 ± 9	22 ± 7	14 ± 6*	14 ± 6
Sham ECS	39 ± 16	31 ± 8	25 ± 9	18 ± 7	18 ± 6

Data represent mean ± S D latency (seconds) in helpless animals treated with antidepressants for four days

*Lower than helpless controls, $p<0$ 05 by Randomization test

TABLE 6

MEAN ESCAPE FAILURES IN HELPLESS ANIMALS—ALL DRUGS

Condition	Failures	Condition	Failures
Naive controls	3 ± 1	Diazepam (1)	12 ± 4
Helpless controls	13 ± 4	Diazepam (3)	12 ± 4
Imipramine (5)	4 ± 2	Lorazepam (1)	13 ± 4
Imipramine (10)	3 ± 2	Chlordiazepoxide (10)	11 ± 2
Desipramine (5)	3 ± 2	Chlorpromazine (5)	11 ± 3
Desipramine (7)	4 ± 2	Chlorpromazine (10)	12 ± 3
Desipramine (10)	3 ± 2	Haloperidol (2)	12 ± 3
Amitriptylene (5)	3 ± 2	Haloperidol (4)	11 ± 3
Amitriptylene (10)	4 ± 2	Amphetamine (0 5)	11 ± 3
Nortriptylene (10)	3 ± 2	Amphetamine (3)	12 ± 3
Doxepin (10)	3 ± 2	Caffeine (10)	8 ± 2
		Phenobarbital (15)	12 ± 4
Iprindole (10)	3 ± 2	Ethanol (1000)	11 ± 3
Iprindole (15)	4 ± 2	Sham ECS	11 ± 4
Mianserin (5)	3 ± 2		
Mianserin (10)	3 ± 2		
Iproniazid (10)	8 ± 4		
Iproniazid (20)	3 ± 3		
Nialamide (20)	4 ± 3		
ECS	4 ± 2		

Data represent mean ± S D escape failures in 15 test trials Dose of drug in parentheses All antidepressants except Iproniazid (10 mg/kg) are lower than control and no non-antidepressant treatments except caffeine are lower than helpless controls by Randomization test

TABLE 7

PROPORTION OF ANIMALS REMAINING HELPLESS—ALL DRUGS

Condition	Helpless/ Total	Condition	Helpless/ Total
Naive Controls	0/24	Diazepam (1)	7/8
Helpless Controls	10/12	Diazepam (3)	8/8
Imipramine (5)	2/10	Lorazepam (1)	6/6
Imipramine (10)	1/10	Chlordiazepoxide (10)	5/7
Desipramine (5)	2/9	Chlorpromazine (5)	11/12
Desipramine (7)	1/8	Chlorpromazine (10)	6/8
Desipramine (10)	0/8	Haloperidol (2)	5/6
Amitriptylene (5)	1/8	Haloperidol (4)	5/6
Amitriptylene (10)	1/8	Amphetamine (0 5)	10/12
Nortriptylene (10)	0/6	Amphetamine (3)	9/11
Doxepin (10)	1/6	Caffeine (10)	5/6
		Phenobarbital (15)	6/6
Iprindole (10)	0/8	Ethanol (1000)	5/6
Iprindole (15)	1/7	Sham ECS	7/9
Mianserin (5)	0/8		
Mianserin (10)	0/8		
Iproniazid (10)	4/9		
Iproniazid (20)	2/8		
Nialamide (20)	3/10		
ECS	2/8		

Data represent number of animals remaining helpless after four days of drug treatment/total number of animals per group The animals with six or more response failures in 15 trials were defined as helpless Compared to helpless controls, all animals treated with antidepressants except those receiving Iproniazid at 10mg/kg were lower and none receiving non-antidepressants were lower by the Fischer exact probability test

This relatively inconsistent pattern was not observed when mean escape failures over 15 trials was used as the behavioral measure (Table 6) Helpless controls (12±4 escape failures) were clearly different from animals treated with antidepressants (3–4 escape failures), but not from animals receiving other drugs (11–13 failures) Those receiving caffeine were significantly lower than helpless controls, however

Using the criterion of five or fewer escape failures in 15 trials (Table 7), the reversal of learned helplessness by antidepressants is again very clear, with all antidepressant treatments except Iproniazid (10 mg/kg) active and none of the non-antidepressants so

DISCUSSION

The results clearly demonstrate that learned helplessness is reversed by several classes of antidepressant treatment, but not by treatment with a number of agents which are not effective against clinical depression in humans

In the present study, dose-responsiveness in the successful treatments was not demonstrated due to the limited number of doses used and the relatively high doses Such dose-responsiveness was demonstrated previously for imipramine [8] using doses below 5 mg/kg, which is greater than the ED_{50} (3 4 mg/kg for 5 days) determined in that study

Additionally, no data on acute effects are presented, since imipramine [8] could not be demonstrated to reverse helplessness when administered acutely via the intraperitoneal route Within this model system, treatment with drug for several days is required in order for anti-helplessness effects to be achieved

A major feature of the present model lies in the comparison between the effects of stimulants and the MAO inhibitors In both cases, animals treated on a chronic basis were significantly more active and were hyperresponsive to shock in the test situation than were uninjected controls The major difference between the groups receiving MAO inhibiton and stimulants lay in the goal-directed nature of the responses in the test situation While animals given the stimulants had more random lever presses than those given other drugs, they failed to establish a consistent pattern of responding with the lever For example, the group given caffeine averaged 7 6±2 4 escape failures Compared with the 13 2±3 0 failures observed in helpless animals, this value is significantly lower However, only one of the six animals in this group had fewer than six escape failures, the upper limit of control responses This difference between controls and caffeine-injected animals is not statistically reliable when measured by the Fischer's exact probability test Thus, it can be shown that drugs which increase shock responsiveness (e g , stimulants) do have a behavioral effect in reducing the number of high-latency responses through random responding, but do not return behavior to control levels, as is

the case with antidepressants It is with this class of compounds (stimulants), however, that the greatest probability of "false positives" might reasonably occur if this test is used for screening of new compounds

Another potential aspect of the model which would tend toward the obtaining of "false positives" lies in the failure of all animals which are exposed to helplessness training to become helpless Only about 85% of the rats trained by this paradigm (e g , 10 of 12 saline-treated animals or 84%) remained helpless when tested five days later Thus, a reversal rate of about 15% can be anticipated when inactive compounds are tested This is seen, for example, with animals given 1 mg of diazepam/kg, (88%) haloperidol (84%), amphetamine (82%), or ethanol (83%) Clearly, this failure of the model system must be taken into account in evaluating the reversal of helplessness

The mechanism by which exposure to uncontrollable shock produces the behavioral deficit described as helplessness is undefined, but has been attributed to norepinephrine depletion, acquisition of immobility, "emotional exhaustion," serotonin depletion, stress-induced analgesia or to one of several cognitive factors The purpose of this study was not to attempt to define which factors are operative, or which were affected by antidepressant treatments, but simply to assess whether the model system could be demonstrated to have adequate pharmacological selectivity towards antidepressants to allow its use in further studies of the actions of antidepressants

In spite of numerous drawbacks, the helplessness model can be shown to have reasonable reliability and specificity These features make it a useful tool for the study of antidepressants, and the similarity between an increased number of escape failures and "psychomotor retardation" in humans suggests additional utility as a model of some aspects of depression in humans

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