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Action of Di-n-propylacetate on the Spontaneous and Acquired Behaviour in Goldfish, Mice and Rats

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MISSLIN, R., P. ROPARTZ AND P. MANDEL. *Action of di-n-propylacetate on the spontaneous and acquired behaviour in goldfish, mice and rats.* PHARMAC. BIOCHEM. BEHAV. 4(6) 643–646, 1976 – The action of n-dipropylacetate (nDPA) is related to the dose. In low doses, nDPA improved the number of conditioned responses with negative reinforcement. In higher doses, the drug inhibited spontaneous and conditioned behaviour. As nDPA produces an increase in gamma-aminobutyric acid (GABA) brain level, results are discussed in relation to the inhibitory action of GABA in the central nervous system.

N-dipropylacetate Gamma-aminobutyric acid Locomotor activity Operant conditioning

MISSLIN, R., P ROPARTZ AND P. MANDEL. *Les effets de l'acide di-n-propylacétique sur des comportements spontanés et acquis chez le poisson Carassius auratus, la souris et le rat* PHARMAC. BIOCHEM. BEHAV. 4(6) 643–646, 1976. – L'action du n-dipropylacétate (nDPA) est fonction de la dose. A faibles doses, le nDPA augmente le nombre des réponses conditionnées avec un renforcement négatif. A des doses plus fortes, la substance inhibe le comportement spontané et conditionné. Dans la mesure où le nDPA augmente le taux cérébral de l'acide gamma-aminobutyrique (GABA), les résultats sont discutés en liaison avec l'action inhibitrice du GABA dans le système nerveux central.

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SEVERAL experiments indicate that GABA has an inhibiting effect on animal behaviour. Injected into cats, it reduces their defensive reactions and improves their sociability, it also decreases their spontaneous and conditioned activity [5] In rats it decreases the number of conditioned responses [1] The level of brain GABA increases during sleep [6] However, these observations are too fragmentary to demonstrate the specificity of GABA in animal behaviour In particular, it seems impossible at present to directly relate the inhibitory effect of GABA on behaviour with its inhibitory effect on certain nervous pathways

It has been recently proved that branched brain fatty acids such as dipropylacetic acid increase the level of brain GABA, not by modifying the turnover of GABA from glutamic acid, but by a competitive inhibition of GABA-transaminase that converts GABA into succinic semialdehyde [2, 3, 11]. These substances are deprived of toxic effects whereas substances used before, such as hydroxylamine or amino-oxyacetic acid, are toxic.

In this paper, we describe the effects of n-dipropylacetate (nDPA) on spontaneous and conditioned behaviour in goldfishes, rats and mice. Some of these results have already been published [8,12], but no general view of this question has been established

METHOD

Acquisition of Conditioned Reactions with Negative Reinforcement

Goldfish Forty goldfishes (*Carassius auratus*) assigned to 4 groups of 10 fishes (11–12 cm) were kept in individual tanks for one month before test. The tanks were constantly filled with running water (pH = 7.5), at about 20°C. The fishes were fed with tubifex

An apparatus based on that of HORNER *et al* [4] was used for conditioning. It consisted of a Plexiglas tank (27 × 10 × 15 cm), divided into 2 equal compartments by a barrier 4 cm high, the water level was 6 cm. The goldfishes were trained to avoid an electric shock (1.5 V) which was delivered by a grill placed on the side of the tank

The testing session consisted of 5 series of 4 trials A trial consisted of a 20 sec stimulus light in the compartment occupied by the fish, followed by the addition of electric shock, after which darkness was restored. Four trials were

separated from the following series by an interval of 5 min A correct response was counted if a fish avoided shock by swimming out of the lighted compartment before the electric shock. For 3 successive days, each fish was submitted to 20 trials per day. NDPA was administered to the fish in water containing the drug during 3/4 hr before test The doses used were 3 mg, 15 mg and 30 mg/l. Ten fishes were tested at each dose

Swiss mice Fifty 6 week old male mice, raised in groups of 5 since weaning, were conditioned in a Mowrer-Miller cage in a single session of 100 trials. The warning stimulus was a 6 sec buzzer (1000 Hz, 75 dB). If the animal crossed the shuttle box barrier during the 3 first sec, an avoidance response was counted. The electric shocks (40 V) were given by a floor grid. The animals were assigned to 5 groups of 10. The doses used were 70, 100, 200 and 400 mg/kg Each animal was given 0 3 ml per 30 g of a nDPA solution, the controls were given 0.9% NaCl. The injections were given intraperitoneally, 30 min before test

Rats Sixty 10 week old male Wistar rats were conditioned in a Mowrer-Miller cage in a single session of 150 trials The experimental procedure was similar to that described for the mice. The animals were divided into 6 groups of 10. They were injected with 100, 200, 300, 400, or 500 mg/kg nDPA or saline alone (1 ml/250g).

Acquisition of Conditioned Responses with Positive Reinforcement

Mice Thirty-nine 6 week old male Swiss mice were conditioned in Skinner boxes. The reward was buckwheat seeds The animals placed in a cage (15 x 15 x 20 cm) access to food by pressing a pedal. The mice were starved for 24 hr before test. Between sessions, they were given a 3 g food cake. Each animal was tested 1 hr per day for 5 successive days with a schedule of continuous reinforcement The animals were divided into 3 groups of 15, 15 and 9 given 0, 100 and 400 nDPA respectively. The injection was given intraperitoneally, 30 min before each session

Rats. Thirty-six 2 month old male Wistar rats were conditioned in Gerbrands 51000 type Skinner boxes, with a schedule of continuous reinforcement, consisting of 45 mg food pellets The animals were starved for 24 hr before test They were tested in a single session of 2 hr. The animals were divided into 3 groups of 12 and given 0, 100 and 400 mg/kg nDPA IP 30 min before test.

Spontaneous Activity

Mice An actograph equipped with photo-electric cells recorded the spontaneous activity of 30 male and female 6 week old Swiss mice. The apparatus consisted of a Plexiglas cage (130 x 23 x 21 cm) Five photo-electric cells were fixed to the back wall, 20 cm apart and at 3 cm from the floor The animals were divided into 5 groups of 12 and respectively given doses of 0, 100, 200, 300 and 400 mg/kg nDPA Each animal spent 2 hr in the actograph immediately after the injection of the drug IP A counter recorded the number of passages of the animal in front of the photo-electric cells.

Rats Sixty Wistar rats, divided into 6 groups of 10, were placed in an actograph similar to that used for the mice. The doses used were 0, 100, 200, 300, 400 and 500 mg/kg.

RESULTS

The Effects of nDPA on Conditioning with Negative Reinforcement

Goldfish nDPA significantly ($p<0.01$) increased number of conditioned avoidance reactions in animals dosed with 3 mg/l on the first day, whereas nDPA significantly decreased ($p<0.05$) performances in animals dosed with 15 and 30 mg/l on the third day of testing (Fig 1). (Statistical test will be indicated every time that it differs from variance analysis).

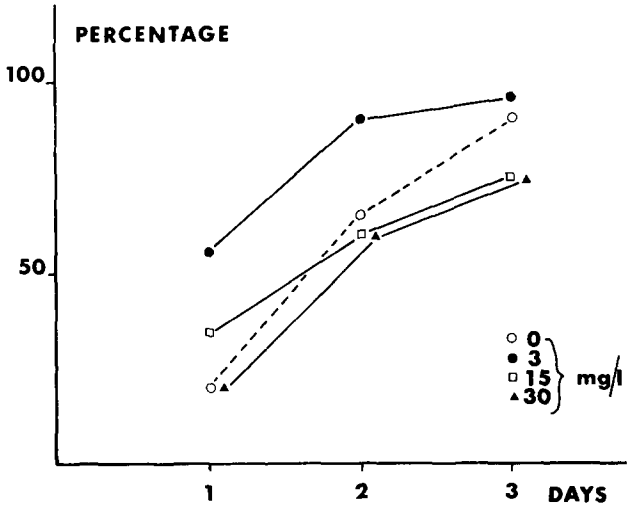

FIG. 1. Acquisition of avoidance responses in goldfish. Mean percentage of conditioned responses. Animals received 20 trials on 3 successive days.

Mice nDPA significantly improved the number of conditioned avoidance reactions in mice dosed with 70 mg/kg ($p<0.02$), 100 mg/kg ($p<0.001$) and 200 mg/kg ($p<0.01$). Furthermore, nDPA at 400 mg/kg significantly reduced the performance ($p<0.001$) (Fig. 2)

Rats nDPA increased significantly the number of avoidance responses in rats dosed with 100 mg/kg ($p<0.001$) and 200 mg/kg ($p<0.01$), whereas it decreased them in animals dosed with 500 mg/kg ($p<0.05$) (Fig. 3)

Effect of nDPA on Conditioned Responses with Positive Reinforcement

Mice nDPA decreased significantly ($p<0.02$) the number of pressing responses in animals injected with 400 mg/kg, whereas animals dosed with 100 mg/kg showed no difference with controls. (Fig. 4).

Rats nDPA has the same effect in rats as in mice it decreased significantly ($p<0.001$) the number of conditioned responses in animals dosed with 400 mg/kg and had no effect in animals dosed with 100 mg/kg (Fig 5)

Effects of nDPA on Spontaneous Activity

Mice nDPA decreased spontaneous activity in mice with all doses. However the difference between the activity in treated animals and controls is only significant with 300 mg and 400 mg/kg (Table 1).

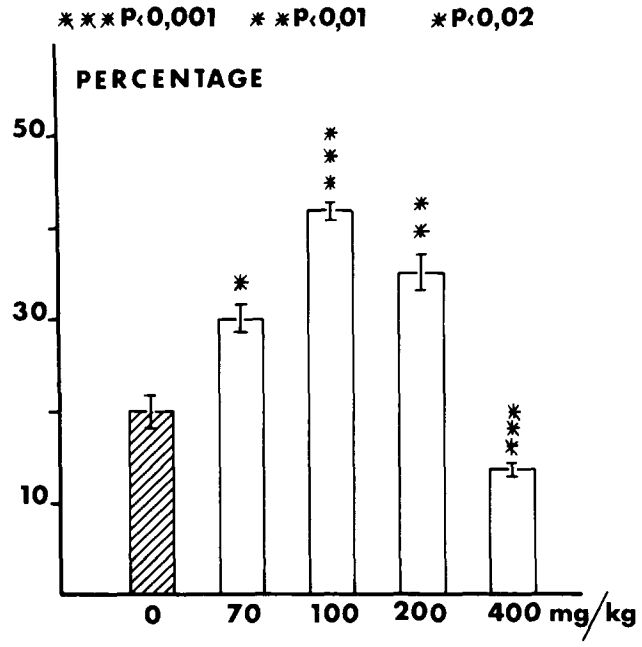

FIG. 2. Mean percentage and standard error of avoidance performance in mice. Animals received 100 trials on one day.

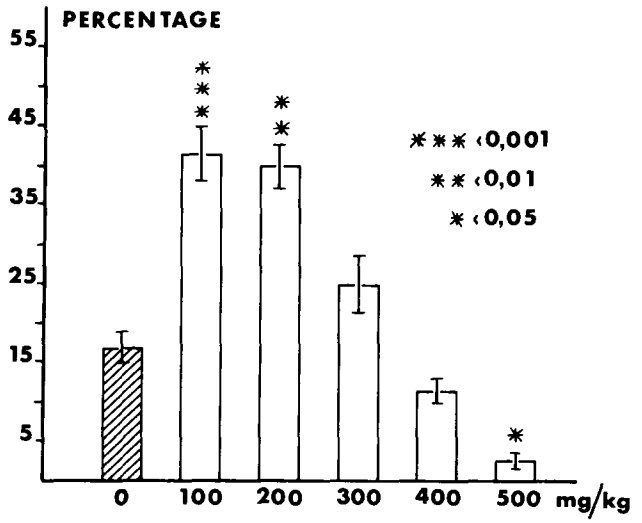

FIG. 3. Mean percentage and standard error of avoidance responses in rats. Animal received 150 trials on one day.

Rats The same results were observed in rats nDPA decreased spontaneous activity in the treated animals function to doses (Table 2). The slope of the regression line significantly differs from a null slope ($p<0.02$) A dose depending effect is thus observed.

DISCUSSION

The present results demonstrate that the injection of high doses of nDPA always reduced locomotor activity and conditioned behaviour High doses of nDPA produced an important neuromuscular relaxation which might explain the great reduction of behavioral patterns after these doses However, this myorelaxan effect does not seem sufficient

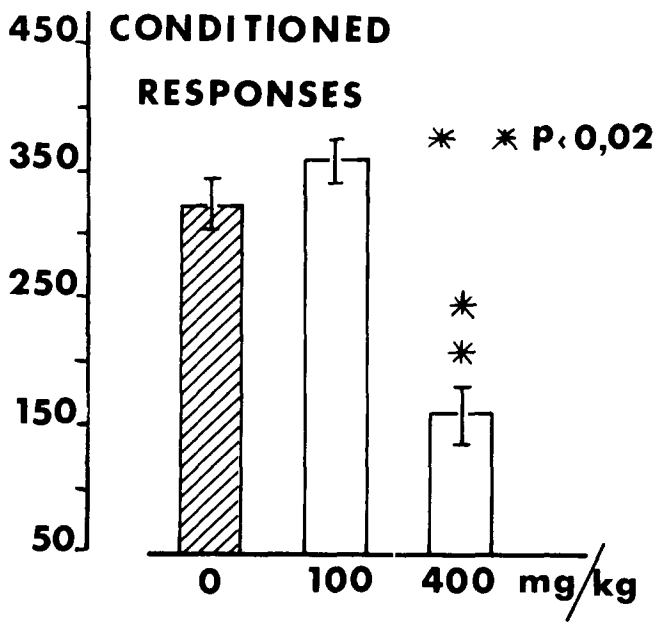

FIG. 4. Effects of nDPA on acquisition of conditioned reponses with positive reinforcement. Mean number and standard error of pressing responses in mice.

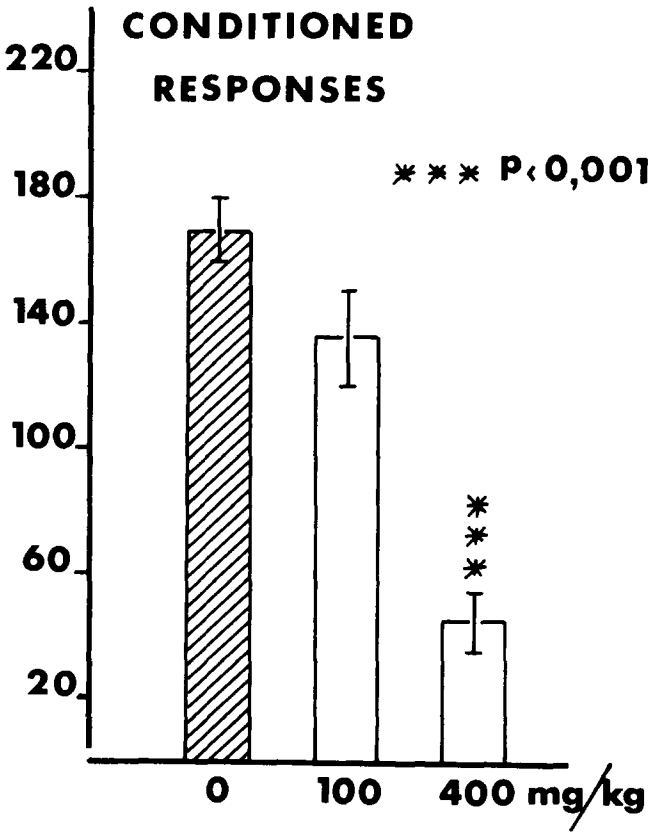

FIG. 5. Effects of nDPA on acquisition of conditioned responses with positive reinforcement in rats. Mean number and standard error of pressing responses.

TABLE 1

ACTION OF nDPA ON LOCOMOTOR ACTIVITY IN MICE MEAN NUMBER AND STANDARD-ERROR OF PASSAGES OF ANIMAL IN FRONT OF THE PHOTO-ELECTRIC CELLS A DOSE DEPENDING EFFECT IS OBSERVED ($F = 15.54$, $p<0.001$)

Doses mg/kg	0	100	200	300	400
Mean	1125	964	998	823	534
Standard-error	115	133	102	83	94
N	12	12	12	12	12

TABLE 2

ACTION OF nDPA ON LOCOMOTOR ACTIVITY IN RATS MEAN NUMBER AND STANDARD-ERROR OF PASSAGES OF ANIMAL IN FRONT OF THE PHOTO-ELECTRIC CELLS A DOSE DEPENDING EFFECT IS OBSERVED ($F = 5.77$, $p<0.02$)

Doses mg/kg	0	100	200	300	450	500
Mean	322	302	322	262	217	192
Standard-error	59	37	61	59	37	31
N	10	10	10	10	10	10

to explain all changes in behaviour, since animals continue to escape electric shocks, but do no longer avoid them The possibility is raised that high doses of nDPA depress the CNS, in particular the vigilance centres, thus explaining reduction of locomotion and conditioned responses Since administration of nDPA increases brain GABA in rats and mice, the inhibitory action of nDPA might be related to the already known inhibitory effects of GABA on behaviour

Low doses of nDPA had no apparent effect on locomotor activity and conditioned responses with positive reinforcement, whereas they increased number of conditioned avoidance responses. The latter effect is in accordance with our recent findings. in mice, nDPA, in the dose of 100 mg/kg, has a facilitating action on the acquisition of conditioned avoidance reactions in another experimental situation [9] Furthermore, we have found that the same dose of nDPA increased exploratory activity observed in open field test [10]. Since these experimental situations cause emotional reactions, we hypothesize that the dose of 100 mg/kg reduced these aversive effects and thus facilitated learning and exploration

In summary, it appears that high doses of nDPA reduced spontaneous and conditioned responses whereas low doses had apparently some anxiolytic action and improved learning and exploration in aversive situations

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