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Amineptine Improves the Performance of Dogs in a Complex Temporal Regulation Schedule

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BRUHWYLER, J., E. CHLEIDE, M. C. RETTORI, J. C. POIGNANT AND M. MERCIER. *Amineptine improves the performance of dogs in a complex temporal regulation schedule.* PHARMACOL BIOCHEM BEHAV 45(4) 897–903, 1993.—Amineptine is a tricyclic antidepressant with activating properties, that stimulates spontaneous locomotor activity in rodents and elevates mood in humans. It mainly inhibits dopamine uptake and weakly increases dopamine release. Formulating the hypothesis that this drug would decrease waiting capacity, we decided to test amineptine in a Differential Reinforcement of Response Duration schedule (DRRD 9 s Limited Hold 1.5 s) in the dog. The drug was administered orally at 2.5, 5.0, 7.5, 10 and 20 mg/kg, 1 h before the experimental session. Between 2.5 and 10 mg/kg, amineptine improved the performance by increasing the response (nonsignificantly) and reinforcement (significantly) rates and by increasing the peak of correct responses (significantly). The inverse effect was measured for the reinforcement rate (nonsignificantly) and for the peak of correct responses (significantly) at the dose of 20 mg/kg. These results were compared to those obtained with other classes of drugs, like neuroleptics, barbiturates or anxiolytics, that disturbed the performance, and particularly with low doses of neuroleptics, which also increase the dopamine release. The positive effects of amineptine on performance (2.5–10 mg/kg) were related to its inhibitory effect on dopamine uptake and discussed in terms of improved vigilance and attention, increase of waiting capacity, improved anticipation, and cognitive enhancement.

Amineptine Tricyclic antidepressant Cognition Temporal regulation Improved anticipation Dog Dopamine

AMINEPTINE is a fast acting (7 days) tricyclic antidepressant drug (19) with activating properties which selectively inhibits neuronal dopamine (DA) uptake (5,38) and which displaces in vitro and in vivo ^{3}H-GBR 12783 binding, a selective ligand for the DA uptake site (12). In high doses, it has also a DA-releasing activity (33). It has neither anticholinergic nor cardiovascular or sedative side effects (27). It stimulates spontaneous locomotor activity in rodents (13). Amineptine antagonizes signs of depression induced by reserpine such as hypothermia, ptosis, and catalepsy (6,31) and reduces immobility in the Porsolt's test (6). Clinically, many open and double blind studies have demonstrated the antidepressant efficacy of amineptine (150–250 mg/day) (37), especially in forms of depression where anergy and inhibition predominate (18,19, 23,34,39).

It has frequently been observed that on differential reinforcement of low rate of response (DRL) schedules, requiring animals to let a specified time elapse between successive operant responses to obtain food reward, conventional and atypical antidepressant drugs improve performance by increasing the reinforcement rate and decreasing the response rate (24,28,29). However, atypical antidepressants with stimulant properties in rodents, nomifensine (29), bupropion (40) and amineptine (22), produced the inverse effect by increasing response rate and decreasing reinforcement rate. In another model in which rats were allowed to choose between a large-but-delayed reward and a small-but-immediate reward in a T-maze, antidepressants increase the frequency of choice of the large-but-delayed reward (3,44). According to Thiébot et al. (44), these experiments indicate that antidepressants may enhance waiting capacity (i.e., improve impulse control). To our knowledge, amineptine has not been tested in this procedure but it could be hypothesized that its disinhibitory properties would not be compatible with an enhanced waiting capacity.

To evaluate this hypothesis, amineptine has been tested in the dog, in a complex operant procedure of differential reinforcement of response duration (DRRD) with external cues (8,25). The DRRD schedule is more restraining than DRL because it requires the inhibition of all the behavioral patterns incompatible with holding the response (21). This procedure has successfully been used in previous studies to differentiate

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barbiturates, anxiolytics, typical and atypical neuroleptics (9,10). Barbiturates and benzodiazepines increased response rate at low doses and reduced it with higher doses while neuroleptics lowered the response rate at all doses in a dose-dependent manner. Reinforcement rates were always decreased whatever the drug (barbiturate, benzodiazepine, or neuroleptic) and the dose. With low doses of neuroleptics (haloperidol 0.01-0.1 mg/kg, sulpiride 5-15 mg/kg), a nonsignificant decrease in response rate was accompanied by a shift to the left in the temporal distribution of response durations (11), thus corroborating the behavioural disinhibition detected in other procedures with low doses of antipsychotic drugs (14,30). It was difficult to invoke a general increase in activity or excitation to interpret those effects, as it was the case for benzodiazepines or stimulants, because here there were accompanied by a decrease in response rate. However, these disinhibitory properties of low doses of neuroleptics (haloperidol and sulpiride) seemed consistent with a release of DA induced by a presynaptic dopaminergic antagonism (11). Because the increase in the release of DA is a common effect of both neuroleptics (for low doses) and amineptine (for high doses), a comparison in the effects of both drugs was justified in this paradigm.

MATERIALS AND METHODS

Subjects

Six conditioned male Beagle dogs (5 years old); weighing from 13 to 16 kg and drug-free since 3 months were used in these experiments. They were housed in separate cages and fed after the afternoon session with Cervo Expan diet (250 g).

Test Room

The size of the test room was 5.6 × 3.5 m. At the entrance, in the right-hand corner there was a board (60 × 50 × 2 cm) fastened to the ground. In the opposite corner, the food dispenser (50 × 76 × 52 cm) was situated. The auditory signals for the test were emitted from two loud-speakers incorporated in the ceiling. Water was available throughout the session. The experimenter stood in an observation cabin fitted with two-way mirrors. The booth contained all the controls of the external stimuli and the distribution of reinforcements, as well as the materials for observing and recording the sessions. The experiment was controlled by computer (PDP 11/73).

Procedure

The procedure has been described previously (8,10,11). Briefly, it was a DRRD schedule with limited hold (LH) and positive and negative external cues. It consisted of the random alternation of two kinds of trials. A maintenance response lasting 9 s on the board was required for obtaining reinforcement. At the end of this time delay, an auditory stimulus of 1.5 s was given to the animal. Every time it left the board between 9 and 10.5 s and then jumped on the food dispenser, it received a piece of meat (5 g). In the second type of trials an additional similar auditory stimulus was randomly presented between the 3rd and the 6th s of the time delay. Both auditory stimuli were physically identical and had the same duration (1.5 s); the animal could only discriminate between them according to their location in time. Both kinds of trials were presented in an equal number and were distributed randomly during the session. Thus the added stimulus was double random, first, because it was not given on each trial and, second, because it was given at random between 3 and 6 s. In every case, the only reinforced response was the response to the stimulus at 9 s, any anticipated (<9 s) or delayed (>10.5 s) response was not reinforced. The unit of behavior requiring reinforcement was twofold and consisted of a locomotor inhibition response lasting 9 s, followed by a locomotor response and a jump on to the food dispenser, which terminated the

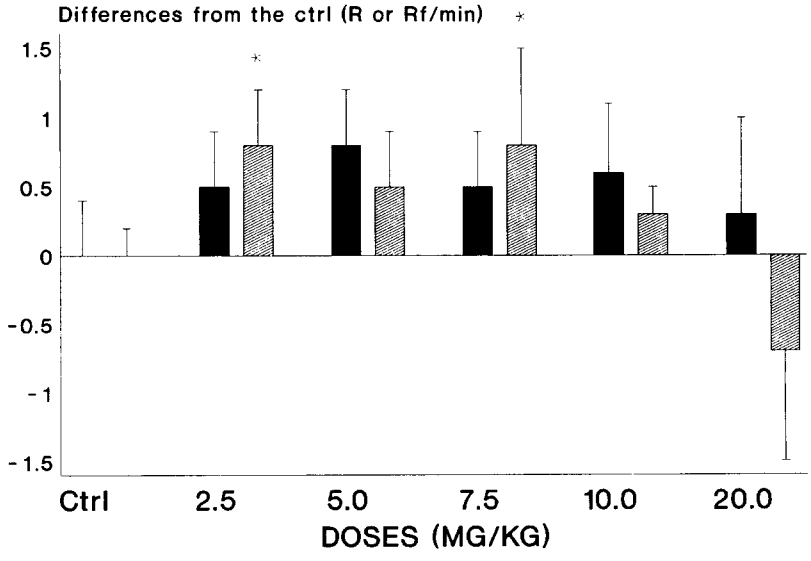

FIG. 1. Effects of amineptine on the difference score data between the average baseline session and the drug treatments for the total response rate (■) and reinforcement rate (□) R/MIN : responses per minute; Rf/min : reinforcements per minute; *$p <$ 0.05 Dunnett's t test; error bars : standard deviation.

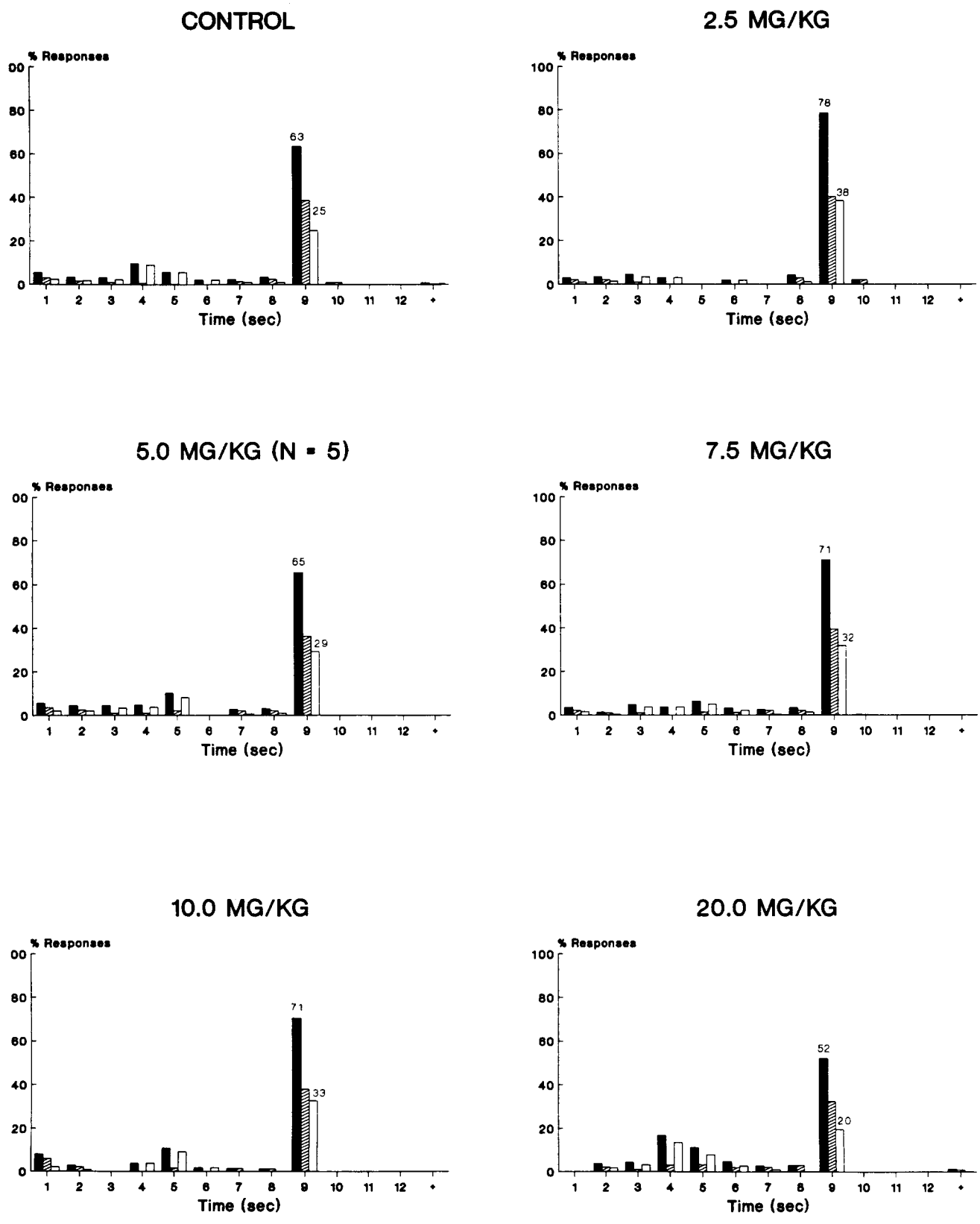

FIG. 2. Effects of amineptine on the temporal distributions of response durations compared to the average baseline session (average of 5 days, each day taken before drug administration). Trials with the negative stimulus between 3 and 6 sec (white), trials without the negative stimulus (hatched) and pooled trials (black).

operant sequence. Experimental sessions were limited by the subject obtaining 8 reinforcements and/or by a maximum time of 900 s. Performance was considered stabilized when 60% of responses were correct (after 30 sessions).

Drug Administration

After stabilization of performance, amineptine chlorhydrate (Servier; 2.5, 5.0, 7.5, 10, and 20 mg/kg) was administered orally in capsule form with each dose being given every 2 weeks in a random order (10, 20, 5, 2.5, 7.5 mg/kg). The experimental sessions took place 1 h following drug administration. On the day before drug administration, the subjects received a placebo (capsule containing talc) and took part in a control session 1 h later. The doses were chosen to correspond with those used in man (150–250 mg/day) (37), and those previously tested in rats and monkeys (31). The 1-h delay between drug administration and session was chosen according to the pharmacokinetic parameters of amineptine in the dog (31,36).

Statistical Analysis

An analysis of variance (ANOVA) for repeated measures with the factor "dose" as classification criterion was used to evaluate the effects of amineptine on total response rate and reinforcement rate. The test was realized on the baseline-treatments difference score data. When significant ($p < 0.05$), it was followed by posthoc Dunnett's t-tests (48). Subject 6 was discarded before the administration of 5 mg/kg because of a wound of the paw. This same subject was discarded from all ANOVA treatments to equalize the sample sizes ($n = 5$). The Kolmogorov-Smirnov's test was used to compare the temporal distributions of response durations.

RESULTS

The average baseline response rate calculated on the 5 control days (each day before drug administration) was 3.20 responses/min. The effect of the pharmacological treatment on total response rate was nonsignificant ($p > 0.05$). Irregular increases were observed with a maximum for 5 mg/kg (Fig. 1). The average baseline reinforcement rate calculated on the 5 control days (each day before drug administration) was 2.25 reinforcements/minute. The effect of the factor "dose" on reinforcement rate was significant [$F(5, 24) = 6.39$; $p < 0.01$]. The increase was significant ($p < 0.05$) for 2.5 and 7.5 mg/kg (Fig. 1). For 20 mg/kg a nonsignificant decrease in reinforcement rate was measured.

The evolution of the temporal distribution of response durations as a function of the dose is shown of Fig. 2. For the average baseline session, there was a peak of 63% situated at 9 s corresponding to correct responses. The majority of errors were produced before 9 s. The distribution was significantly modified by amineptine for 2.5 ($K_d = 16.2$; $p < 0.01$), 7.5 ($Kd = 8.1$; $p < 0.05$), 10 ($K_d = 7.2$; $p < 0.05$) and 20 mg/kg ($K_d = 12.1$; $p < 0.01$) but not for 5 mg/kg ($p > 0.05$). For 2.5, 7.5 and 10 mg/kg, the principal mode centered on 9 s increased to 78%, 71% and 71% respectively. This improvement of performance was not accompanied by a general shift to the right since no delayed (>10.5 s) response durations were measured. For 20 mg/kg, the distribution was disturbed. The peak of reinforced responses was reduced (52%) to the advantage of disinhibitory errors produced between 3 and 6 s, the moment at which the negative stimulus was delivered. The temporal distributions of response durations for the trials without the auditory stimulus between 3 and 6 s were not

TABLE 1

EFFECTS OF AMINEPTINE ON THE TEMPORAL DISTRIBUTIONS OF RESPONSE DURATIONS FOR THE DIFFERENT SUBJECTS

Time (s)		1	2	3	4	5	6	7	8	9	10	11	12	+	K_d
Subject 1	Control (mg/kg)	5	2	3	15	2	4	0	5	61	1	0	0	2	
	2.5	3	2	7	3	0	2	0	3	78	2	0	0	0	16†
	5.0	5	5	2	4	10	0	1	6	68	0	0	0	0	10†
	7.5	4	1	5	0	5	7	3	2	71	1	0	0	0	15†
	10	15	0	0	1	10	3	1	0	70	0	0	0	0	10†
	20	0	2	5	10	15	2	2	3	58	0	0	0	2	7*
Subject 2	Control (mg/kg)	9	2	3	12	9	2	5	2	55	0	0	0	1	
	2.5	8	2	0	1	0	4	0	6	76	3	0	0	0	27†
	5.0	8	2	6	8	13	0	5	2	56	0	0	0	0	2^{NS}
	7.5	7	2	0	7	9	3	6	4	62	0	0	0	0	10†
	10	7	3	0	3	6	2	4	1	74	0	0	0	0	17†
	20	0	4	9	17	13	6	3	0	48	0	0	0	0	12†
Subject 3	Control (mg/kg)	6	7	5	10	3	0	2	3	64	0	1	0	1	
	2.5	6	4	5	0	0	0	0	0	84	1	0	0	0	21†
	5.0	2	7	2	9	8	0	3	0	69	0	0	0	0	8*
	7.5	2	2	7	3	2	0	3	2	79	0	0	0	0	15†
	10	12	3	0	3	6	1	0	0	75	0	0	0	0	11†
	20	0	5	3	25	15	8	0	0	42	0	0	0	2	25†

Results are given as % of responses; K_d Kolmogorov-Smirnov's value; NS = not significant.
*$p < 0.05$; †$p < 0.01$.

significantly different from the baseline whatever the dose ($p > 0.05$). On the other hand, they were significantly modified for the trials with the stimulus at 2.5 mg/kg ($K_d = 13.4$; $p < 0.01$), 7.5 mg/kg ($K_d = 7$; $p < 0.05$) and 10 mg/kg ($K_d = 9$; $p < 0.01$) (Fig. 2).

Table 1 showed the individual temporal distributions of response durations as a function of the dose. For subjects 1, 3 and 4, all the distributions were significantly ($p < 0.05$ or $p < 0.01$) different from their corresponding baseline. The peak of correct responses (9 sec) increased between 2.5 and 10 mg/kg and decreased for 20 mg/kg. The same observations could be made for subjects 2 and 5 with the exception of one dose (5 mg/kg) for which their distributions were not significantly modified ($p > 0.05$). The temporal distributions of response durations of subject 6 were not affected at 2.5 and 7.5 mg/kg ($p > 0.05$) but significantly disturbed for the two higher doses ($p < 0.01$).

DISCUSSION

Contrary to the observations made in DRL with DA uptake inhibitors (nomifensine, bupropion and amineptine) (22, 29,40), amineptine did not lead to a deterioration of performance in this study. Indeed, it contributed to a significant improvement of performance between 2.5 and 10 mg/kg with the exception of 5 mg/kg for which subjects 2 and 5 were not significantly affected by the drug. Contrary to the response and reinforcement rates for which the variability was high, the changes in the temporal distributions of response durations showed a higher homogeneity from one subject to the other. Indeed, only subject 6 did not react in the same way as other subjects. Amineptine increased the response rate (nonsignificantly) and the reinforcement rate (significantly) and produced a better adjustment of the temporal distribution of response durations with an increase in the peak of correct responses but without a general shift to the right beyond the required delay. This profile of action has nothing to do with neuroleptics that decrease response and reinforcement rates and seriously disturb temporal regulation by producing a complete shift to the right or with anxiolytics and barbiturates that increase response rate but decrease reinforcement rate and disturb temporal regulation by producing a complete shift to the left (9,10). It is also different from the positive effects of antidepressants on reinforcement rate measured in DRL (24,41). According to Howard and Pollard (17), nonantidepressant treatments that reduce response rate without affecting the physical capacity to respond would likely mimic the antidepressant effect. So did a reduction in hours of deprivation (32). It means that treatments that reduce responses moderately are likely to increase reinforcements. In our procedure, amineptine induced the same effect on reinforcement rate without decreasing the response rate. Moreover, a characteristic shift to the right in the temporal distribution of responses is generally observed with antidepressants (35). Such a shift would produce a negative effect on reinforcement rate in our procedure because responses are reinforced only when they are emitted between 9 and 10.5 s. So a nonspecific shift to the right is not appropriate to take into account the improvement of performance. The fact that amineptine significantly improved the temporal distribution of response durations for the trials with the negative stimulus presented between the 3rd and the 6th s without modifying the other trials, also attests of a specific mechanism rather than a nonspecific shift to the right. The temporal discrimination task used in this study is similar to a DRL schedule, in that the task requires subjects to make a temporal discrimination and to withhold a response. However, it differs from a classical DRL in that the subjects have to inhibit all the behavioural patterns incompatible with the maintenance response on the board. Moreover, they have also to correctly discriminate external cues on the basis of their temporal regulation. These methodological differences and the use of the dog as experimental subject, instead of the rat, could explain the differences observed in the effects of amineptine in DRL and in our procedure. The present results should be considered as basic psychopharmacological informations and not as predicting or reflecting antidepressant activity. To further investigate this hypothesis, the test of other atypical antidepressants, like bupropion and nomifensine, but also of classical antidepressants and MAO inhibitors should certainly be undertaken in the future. It could be particularly interesting to test such compounds in a chronic crossover design that approximates the therapeutic course in the clinic.

The increase in correct responses (rate and percentage) could be accounted by an improved vigilance and selective attention like it has been noted in humans treated with amineptine (7,18) or by an enhanced waiting capacity, that is, improve impulse control (3,44). This is particularly the case in our procedure when the subject has to inhibit its behavior in response to the negative stimulus. Moreover, an increase in the cognitive ability to anticipate the consequence of a response to the negative stimulus (absence of reinforcement) or to the positive stimulus (presence of reinforcement) on the basis of an improved temporal regulation, to better adjust the behavior, could also be postulated. These hypotheses suggest potential cognitive properties of this drug. The existence of cognitive problems in depressive illnesses has been known for many years (16,20,26,45). By correcting the depressive deficit, antidepressants improve or amplify the cognitive problems, according to their pharmacological profile (2). Sedative and/or anticholinergic molecules alter cognition (15), whereas antidepressants without anticholinergic effects improve cognitive functions (46). A pro-cognitive effect has been noted for clovoxamine, nomifensine (43), viloxazine, maprotiline, and moclobemide (2). A cognitive enhancing effect for amineptine would be compatible with its neurochemical properties and its clinical profile (1,7,23).

The effects of amineptine for a high dose (20 mg/kg); that is, no significant effect on response rate, decrease of reinforcement rate, increase of response durations inferior to 9 s, particularly those between 3 and 6 s, are consistent with those previously obtained with low doses of neuroleptics in our procedure (11). The increase of DA-releasing activity is common to high doses of amineptine (33) and low doses of neuroleptics (presynaptic DA_2 antagonism) (42,47) and could explain such a resemblance. However, for low doses of amineptine (2.5–10 mg/kg) the same mechanism can not be invoked. Therefore, the inhibition of DA uptake (5,38) is more likely to be involved in the cognitive enhancing effects of amineptine. Such a hypothesis could be evaluated in the future by comparison with a specific DA uptake inhibitor like GBR 12783 (4,5, 12,13).

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