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Effects of Sulpiride on the Orienting Movement Evoked By Acoustic Stimulation in the Rat

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CRESCIMANNO, G., M. MANNINO, M. CASARRUBEA AND G. AMATO. *Effects of sulpiride on the orienting movement evoked by acoustic stimulation in the rat.* PHARMACOL BIOCHEM BEHAV **66**(4) 747–750, 2000.—Drugs that selectively block D_2 receptors are known to provoke a rapid cell firing increase followed by A9 and A10 dopaminergic (DA) neuron inactivation (depolarization block). In this study, possible relationships between cell firing rapid increase and specific behavioral effects, linked to sensorimotor integration, were investigated in the rat. To this purpose, with the aid of a video camera apparatus and a frame-by-frame analysis, effects of sulpiride-induced blockade of DA D_2 receptors were analyzed on the orienting movement of the head induced by acoustic stimulation. In a control group of rats, during trials lasting 20 min, latency and duration of head turning (HT) were 186.15 ± 51.66 ms and 266.87 ± 47.49 ms, respectively. Sulpiride injection (20,40,100 mg/kg IP) provoked a dose-dependent increase of HT latency and duration; however, only latencies showed statistically significant variations. It is suggested that cell firing rapid increase, observed on A9 and A10 DA neurons, following sulpiride administration, may be correlated to rapid modifications of specific HT parameters linked to sensorimotor integration. © 2000 Elsevier Science Inc.

D_2 receptors Sulpiride Cell firing increase A9 and A10 neurons Head turning Sensorimotor integration Attention Rat

ACCORDING to pharmacologic and clinical data, dopamine has been proved to be involved in the pathophysiology of many forms of psychotic disorders, such as diseases involving attentional or sensory processing abnormalities (8,32). Dopaminergic (DA) D_2-like receptors (D_2,D_3 and D_4) are the primary target in the treatment of psychoses and most antipsychotic drugs block this receptor population in correlation to their clinical potency (15,26,28,29). D_2 receptors are distributed most densily in mesolimbic-mesocortical system and caudato-putamen, whereas D_3 and D_4 ones are prevalently localized in limbic areas (19,30). The former have been suggested to be linked to dopamine modulatory action on sensorimotor function and attentive condition, the latter to the control of cognition and emotion (1,5,6,17).

Among antipsychotic drugs, sulpiride (SULP), a DA antagonist binding selectively to dopamine D_2 and D_3 receptors (26,30), and prevalently acting on mesolimbic-mesocortical DA system (4,13), is one of the most effective in reducing psychotic symptomatology (28,34).

As concerns the achievement of the therapeutic action, even if weeks are required to obtain clear clinical effects, a rapid receptor blockade, following acute antipsychotic administration, has been shown and correlated with the timecourse of rapid modifications observed recording electrophysiologic activity of A9 and A10 DA neurons (9,10,24,29). However, although studies have been carried out in the attempt to search for a correlation between modifications of a given behavior and the delayed antipsychotic-induced midbrain depolarization inactivation (depolarization block) (7,11,18,25,35), the possible link between the very rapid increase in cell firing and recognizable modifications of a given behavior has been poorly investigated.

Aim of the present investigation was to determine whether a relationship between the SULP-induced blockade of D_2 re-

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ceptors, provoking rapid electrophysiologic effect on DA neurons, and rapid modifications of a motor response, triggered by sensory stimuli (sensorimotor integration), may be demonstrated. To this purpose, head turning (HT) movement, induced in the rat by acoustic stimulation, before and after acute administration of different SULP dosages, was studied by means of a videoanalysis apparatus. Because HT is a component of the orienting reaction toward environmental stimuli, i.e., a response needing sensorimotor integration, HT latency and duration can be considered as useful parameters to evaluate modifications of sensorimotor integration speed (22,23,31), that is as sensitive tools to give account of possible rapidly induced behavioral changes.

METHOD

Animals

The study was performed on male wistar rats (250 to 300 g), housed in separate cages (room temperature 21°C), with free access to food and water. Experimental sessions were carried out during the light phase (from 0700 to 1900 h) of the day-night cycle.

Apparatus

Experiments were carried out in a soundproof room, maintained at constant illumination and temperature. Illuminated and ventilated perspex boxes (30 × 30 × 30 cm) were used as observation cages. Two loud-speakers placed within the box walls (one on the left wall and the other on the right one) were controlled by an acoustic stimulator (Coulbourn) whose output switched on a led placed in the front of the cage, indicating, on the monitor, stimulus start and duration. Stimuli (300 Hz, 2 s) were randomly delivered as for spatial localization and intertrial interval (from 1 to 5 min) to avoid habituation; their intensity was checked not to induce avoidance responses.

Behavioral Analysis

Five groups of animals, each composed of 10 rats, were tested during one session only. One group received acoustic stimulation, one was stimulated and received vehicle solution IP, and three groups were stimulated and administered different (±) sulpiride dosages (20, 40, 100 mg/kg IP). Twenty-four hours before trials, the animals were subjected to habituation to the experimental box for 10 min. Experiments were recorded on videotapes by a videocamera apparatus and analyzed via a videocassette recorder. First modification of the studied parameters appeared 5 min after injection; within 20 min the effects began to disappear either the smaller sulpiride dosage was employed or the larger one. Data used in our study concern the animal activity displayed from the 6th to the 20th min. Motor sequence was evaluated on playback in slow motion and frame-by-frame with a temporal resolution of 50 ms. HT latency and duration were calculated analyzing initial and final frame. HT initial time was considered to occur at frame preceding the start of head-orienting movement following acoustic stimulation, and HT final time was considered to occur at frame preceding the end of head movement. Interval between end of acoustic stimulus and beginning of head movement indicated HT latency, and the interval between HT initial and final time indicated HT duration. Experiments were conducted in accordance with the European Communities Council Directive (86/609/EEC) regarding care and use of animals for experimental procedures.

Drugs

(±) sulpiride (Research Biochemicals Inc., Natick, MA, USA) was prepared fresh daily, dissolved in distilled water containing acetic acid 0.1 %, and administered IP in a volume of 5 ml/kg. Control group received the same volume of vehicle.

Statistical Analysis

All values are expressed as means ± SEM. Statistical analysis was performed using one way analysis of variance (ANOVA) followed by the Newman-Keuls (N-K) post hoc test for multiple comparisons. Values of $p < 0.05$ were considered significant. Unpaired Student's *t*-test (two-tailed) was used when the comparison was made between vehicle and only acoustic treated group.

RESULTS

Acoustic stimulation provoked in the rat a head-orienting movement toward stimulus source. Frame-by-frame analysis of responses revealed a sequence of fixed motor acts: auricle erection, coordinated eye deviation, and neck and head torsion. Two specific parameters of the motor sequence were analyzed: HT latency and duration. As to latency, the mean ± SEM was 194.37 ± 64.22 ms and to duration 266.33 ± 53.25 ms. Results, observed in the animals delivered only acoustic stimulation were not significantly modified by vehicle administration (mean ± SEM 186.15 ± 51.66 ms for the latency, $p < 0.91$ unpaired Student's *t*-test, and 266.87 ± 47.49 ms for the duration, $p < 0.99$ Student's *t*-test) (Fig. 1).

Sulpiride administration (20, 40, 100 mg/kg IP) provoked a dose-dependent increase of HT latency and duration when compared with vehicle injected animals. As for HT latencies, the means ± SEM for each dosage were 422.54 ± 76.48 ms,

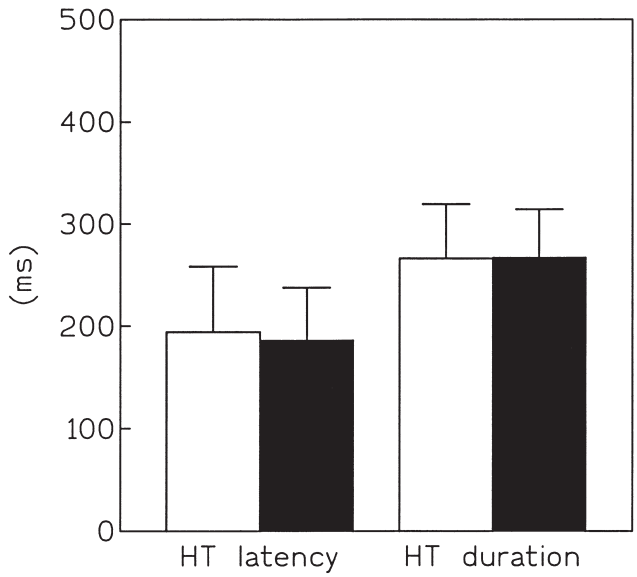

FIG. 1. Comparison between effects of acoustic stimulation alone (blank columns) and acoustic + vehicle solution IP administration (solid columns) on HT latency and duration. Each bar shows mean ± SEM of results obtained from the analysis of 10 animals. All the differences between the two groups are not significant (unpaired Student *t*-test).

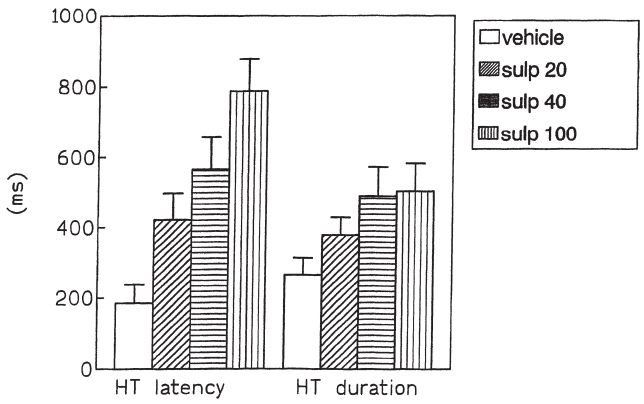

FIG. 2. Effects of different doses of sulpiride (20,40,100 mg/kg IP, hatched columns) and vehicle solution (blank columns) on latency and duration of head turning induced by acoustic stimulation. Each bar shows mean ± SEM of results obtained from the analysis of 10 animals. $p < 0.0001$ for latency and $p < 0.06$ for duration (ANOVA).

566.73 ± 91.06 ms, 789.33 ± 88.52 ms respectively, $F(3, 39) = 10.41$, $p < 0.0001$ (Fig. 2). As for HT durations, the means ± SEM for each dosage were 380.87 ± 48.33 ms, 491.02 ± 83.12 ms, 504.37 ± 79.66 ms respectively, $F(3, 39) = 2.75$, $p < 0.06$ (Fig. 2). Newman-Keuls post hoc comparisons revealed that the three doses of sulpiride produced dose-related increases of HT latency ($p < 0.05$), whereas they failed to induce significant modifications of HT duration. A lack of significance for HT duration, likely due to videoanalysis system time resolution, could not be excluded.

DISCUSSION

Results can be summarized as follows: 1) sulpiride-induced blockade of D_2 receptors increases latency and duration of head turning movement, provoked by acoustic stimulation; 2) these effects appear within 5 min from drug injection and last about 20 min; and 3) latency variations appear highly significant, whereas the duration ones, although close to significance, do not.

It is widely accepted that central DA neurons are important in the response to sensory stimuli, playing a role both in sensory processing and in linked motor response (sensorimotor integration) (22). In limbic and cortical areas (33), and in striatal neurons (14), an increase of dopamine turnover, following different environmental stimulations, has been shown. Moreover, behavioral and pharmacologic studies have suggested a critical involvement of DA neurons in the ability to switch to cue directed behaviors and in orientation behavior (2,5). On the other hand, lesions of caudato-putamen, the nigro-striatal, and the mesolimbic-mesocortical DA systems result in characteristic sensorimotor impairments and attention disorders, with the affected animals unable to integrate sensory informations with the performance of the orienting response (17).

The above evidences suggest some questions: 1) how to evaluate attentive condition and information processing speed, and 2) how antipsychotic drug activity could modify these functions.

If, on the one hand, A9 and A10 DA neurons have been proved to be specifically involved in sensory-gating (12) and orientation behavior (2,5,17), on the other hand, sulpiride exerts a selective effect on D_2 receptors localized in limbic/mesolimbic-mesocortical system. In fact, an increase of DA turnover in limbic and mesolimbic structures, following sulpiride acute and chronic administration (4,13,37) has been demonstrated. Moreover, in behavioral trials, a strong effect on the mesolimbic component of dopamine-mediated behaviors, has been shown (36). In our experimental design acoustically induced HT movement, i.e., a response needing sensorimotor integration (5,22,23,31), was used to analyze the speed of attention shift whose modifications might result in changes of the whole orienting response.

Our study provide evidence that following sulpiride, HT undergoes rapid and recognizable modifications that may be considered as a behavioral expression of the rapid increase in the firing of A9 and A10 DA neurons.

The significant increase of latency may be linked to A10 neurons activity, whose amplification could provoke delayed responses to sensory stimuli, therefore a delayed attention switching. The prefrontal cortex, which has been involved in the regulation of attentive condition (3), has been demonstrated to represent one of the main targets of A10 neurons inhibitory projections (16). This relationship could explain A10 neurons influence on attentive condition. Accordingly, following sulpiride IP, an asynchronous EEG profile, i.e., an activity linked to attention focusing, has been demonstrated in the prefrontal cortex of the conscious rat (27). Because recent data show that drugs, traditionally classified as atypical, activate also nigrostriatal dopamine cells (21), the almost significant increase of HT duration may depend on the simultaneous activation of A9 neurons, which are more directly linked to motor output regulation, in orienting responses (20).

In conclusion, the sulpiride-induced rapid increase of DA cell firing likely influences the animal's reaction by modifying the dopamine-mediated responses to environmental stimuli. Moreover, this behavioral study can be used as a reliable screen available for predicting specific activities of antypsycothic drugs.

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