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BRIEF COMMUNICATION

Loss of Discriminative Avoidance Behavior by Local Application of Kynurenic Acid Into the Nucleus Accumbens of the Rat

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ERICSON, E., T. H. SVENSSON AND S. AHLENIUS. *Loss of discriminative avoidance behavior by local application of kynurenic acid into the nucleus accumbens of the rat.* PHARMACOL BIOCHEM BEHAV **37**(4) 843–845, 1990.—Male Sprague-Dawley rats, trained to perform a visual discrimination, were administered kynurenic acid, an antagonist of excitatory amino acid receptors, 4.7 μg bilaterally into the nucleus accumbens. The performance of the visual discrimination was impaired 15, but not 360, min after administration. In addition, motor activity in the test apparatus was markedly increased by the treatment, whereas no effects were noted when the animals were observed in an open field. The abnormal behavior produced by kynurenic acid has previously been observed after administration of high doses of compounds like *d*-amphetamine and *L*-DOPA, and generally discriminative behavior has been shown to be highly dependent on normal impulse mediated release of dopamine in brain. The present results show that this behavior also is dependent on an intact excitatory amino acid neurotransmission.

Discrimination Avoidance Excitatory amino acids Kynurenic acid Rat

IN a recent report it was demonstrated that the excitatory amino acid (EAA) antagonist kynurenic acid (KA) produce a regularization of firing in rat brainstem dopaminergic neurons (A10) (4). Such changes in firing patterns, in all probability, also produce changes in patterns of dopamine (DA) release (3). It has previously been shown that a nonphysiological DA release, independent of nerve impulses, results in abnormal behavior in rats, as evidenced by a loss of a visual discrimination. In those experiments, the animals were trained to perform a conditioned avoidance response in a conventional shuttle box, with the modification that correct avoidance required attention to a visual discriminative stimulus, in addition to the white noise used as conditioned stimulus (1).

By use of this method, where two aspects of behavior can be studied simultaneously, i.e., discriminative and avoidance performance, we have examined putative qualitative behavioral changes, induced by intracerebral administration of KA in the rat. Kynurenic acid was locally applied into the nucleus accumbens septi (NAS) which receives a prominent innervation from the ventral tegmental area (A10) [e.g., (5)]. Behavioral changes were analysed by observing discriminative behavior and open-field locomotor activity.

METHOD

Animals

Adult Sprague-Dawley rats (ALAB Laboratorietjänst AB, Sollentuna, Sweden) were used. They were housed five in each cage prior to surgery, and individually after surgery, under conditions of controlled temperature (21°C) and relative humidity (50–60%). Food (R3, Ewos, Södertälje, Sweden) and tap water were avail-

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TABLE 1

EFFECTS OF LOCAL APPLICATION OF KYNURENIC ACID INTO THE NUCLEUS ACCUMBENS ON AVOIDANCE LATENCY IN THE RAT

	Latency (s)		
Site	Preinj.	15 Min	6 Hours
Accumbens	2.6 ± 0.4	4.4 ± 0.7*	3.6 ± 2.0†

*$p<0.05$, †$p<0.01$.
For details see legend to Fig. 1. $\chi^2_2=8.75$, $p<0.02$.

able ad lib. The light-dark cycle (12:12 h) was artificially maintained (lights off 06.00).

Apparatus

The animals were trained and tested for the conditioned avoidance behavior in a box made of perspex (530 × 250 × 225 mm), with a grid floor connected to a high resistance power supply. The box was divided into two parts of equal size by a partition with two openings (75 × 80 mm). The experimental chamber was housed in a sound-attenuating, ventilated enclosure, and provided with a dim background light producing approximately 400 lux at the floor level.

Spontaneous motor activity was monitored in a square open-field arena (680 × 680 mm), equipped with infrared-light sensitive photocells spaced 80 mm apart. Locomotor activity was defined as the number of photobean crossings per min using a square root transformation [for further details see (2)]. Observations were made in the dark between 08.30–16.30 h.

Training Procedure

The rats were trained to perform a visual discrimination (successive discrimination), superimposed upon a conditioned avoidance response. In order to avoid the unconditioned stimulus (UCS), an intermittent electric shock (approx. 0.2 mA) in the grid floor, the rat had to choose the correct opening for avoidance, upon presentation of the discriminative stimulus (light, 2 × 75 W bulbs, producing approx. 1900 lux at the floor level), and the CS (white noise, 70 dB). (A) Lights on *plus* CS: Go right, (B) CS only: Go left. CS-UCS interval was 10 s. If the rat failed to avoid within 10 s, or made an incorrect avoidance, the grid shock was presented, and the rat had to make a correct escape to terminate the trial. For further details see (1).

The rats were trained to perform the discriminative avoidance behavior in 10 daily sessions (40 trials per session with an intertrial interval of 15–30 s).

Surgery

After training, the rats were anaesthetized with pentobarbital (60 mg·kg^{-1} IP) and 10 mm guide cannulas (21 ga) were stereotaxically placed bilaterally on the skull. The tips of the guide cannulas touched the dura mater, and were fixed to the skull by means of acrylic dental cement. Coordinates were adopted from the stereotaxic atlas of Paxinos and Watson (6) and bregma was used as the reference point. The following coordinates were used for the nucleus accumbens: AP +1.5, L ±1.2, DV 6.8 mm.

Postoperative Training

Four days to one week following surgery, 1–4 postoperative training sessions were performed, with 1–4 days interval, until the animals performed 80–100% correct avoidance behavior. The postoperative training sessions consisted of 20, randomly distributed, trials (20 trials 7.5 min^{-1}).

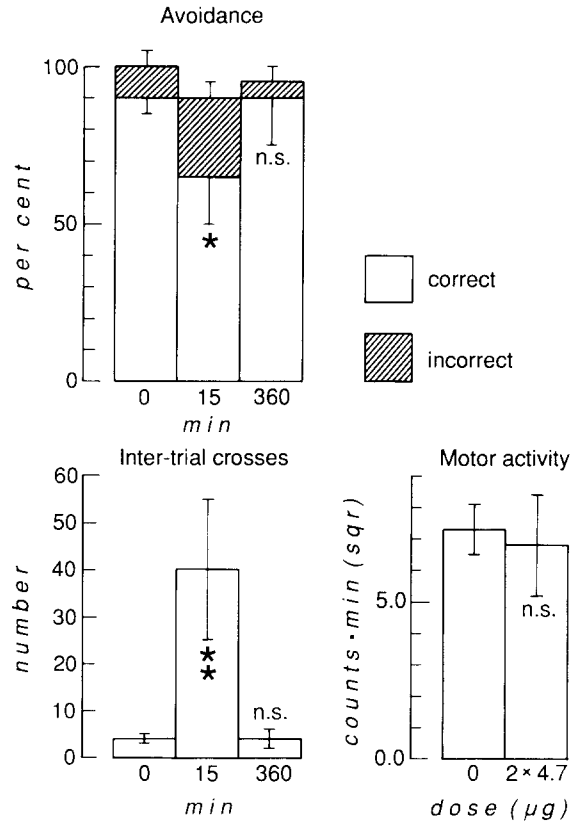

FIG. 1. Effects of local application of kynurenic acid into the nucleus accumbens on discriminative performance and intertrial locomotor activity in the rat. Kynurenic acid was applied, 4.7 μg side^{-1}, into the nucleus accumbens and the animals were observed 15 min and 6 h after the injections. The figure shows median values of avoidance behavior and intertrial crosses ± semi-interquartile range based on repeated observations of 10 rats. Statistical evaluation was performed by means of the Friedman two-way ANOVA, followed by the Wilcoxon matched-pairs signed-ranks test for comparisons with preinjection control performance. $\chi^2_2=7.20$, $p<0.05$ (correct avoidance); $\chi^2_2=8.75$, $p<0.02$ (intertrial crosses). The figure in the lower corner to the right shows the effect of the same kynurenic acid treatment on spontaneous open-field motor activity in a separate experiment. The motor activity is expressed by the means ± SD (n = 6). The Student's *t*-test was used for statistical comparisons. $^{n.s.}p>0.05$, $*p<0.05$, $**p<0.01$.

Test Procedure

The experiments consisted of a pretest immediately before the injections were made by means of a 31 ga injection cannulae (25 ga for the length of the guide and 31 ga for the needle penetrating into the brain). Kynurenic acid (Sigma, St. Louis, MO) was dissolved in basic saline (pH 13) and injected in a dose of 4.7 μg·μl^{-1}, bilaterally into the NAS, at a rate of 0.67 μl·min^{-1} (total volume 1 μl). Preliminary observations indicated that at higher doses, the animals lost tonus and were unable to perform the avoidance behavior.

Test sessions consisted of 10, randomly distributed, trials (10 trials 7.5 min^{-1}). The animals served as their own controls and were tested with an interval of a least 4 days between experi-

ments. The following items were recorded: (A) *correct and incorrect avoidance responding* (which added together make the *total avoidance*); (B) *intertrial crosses* (spontaneous crosses over the midline between CS presentations); (C) *avoidance latency*.

Statistics

The Friedman two-way ANOVA and the Wilcoxon matched-pairs signed-ranks test (7) were used in the statistical evaluations as indicated in the table and the figure.

RESULTS

Effects of Local Application of KA Into the NAS

The local application of KA, 4.7 μg side^{-1}, into the NAS produced a statistically significant decrease in correct avoidance performance and a marked increase in the number of intertrial crosses, 15 min after the injection. These effects had disappeared at the 360-min time interval after the injection (Fig. 1). The avoidance latency was statistically significantly increased at both 15 and 360 min after the injection (Table 1). There were no significant changes, however, in the total avoidance performance, 15 or 360 min after the injection, in comparison with pretest control performance (0 min) ($p>0.05$ at both time intervals). Thus, the decrease in correct avoidance responding was not due to less avoidance behavior, but rather to an increase in incorrect avoidance responding. It should be noted that, at the time of maximal effect of KA on the number of intertrial crosses, no effects were observed on motor activity in an open field (Fig. 1).

DISCUSSION

The present results show that KA, locally applied into the NAS, produced a decrease in correct avoidance responding. This effect is qualitatively similar to effects produced by high doses of *L*–DOPA, apomorphine or *d*-amphetamine, i.e., induced by non-physiological DA receptor activation in the brain. Furthermore, in contrast to the increase in intertrial crosses, produced by KA, no effects were observed on motor activity when the same rats were tested in an open field. Thus, administration of KA was found to selectively impair behavior controlled or activated by sensory stimuli, whereas spontaneous behavior was unaffected. Consequently, the behavioral performance in the discriminative test seems not only to be highly dependent on normal impulse-mediated DA release, but also on functioning EAA neurotransmission in the limbic forebrain. The specificity in the behavioral changes suggests a functional coupling and that EAA may be used to alter dopamine-dependent function, possibly beyond dopaminergic control.

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