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BRIEF COMMUNICATION

Electrical Stimulation of the Dorsal Raphe Nucleus as a Discriminative Stimulus: Generalization to (±)-DOI

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MOKLER, D. J., M. DIXON AND L. STAMBAUGH. *Electrical stimulation of the dorsal raphe nucleus as a discriminative stimulus: Generalization to (±)-DOI.* PHARMACOL BIOCHEM BEHAV **48**(4) 1041–1045, 1994.—Electrical stimulation of the dorsal raphe nucleus of Sprague–Dawley rats was used as the cue for discrimination using a taste aversion paradigm. Rats were trained to associate saccharin drinking during electrical stimulation of the dorsal raphe nucleus with LiCl injection after the session as the aversive unconditioned stimulus. In sessions without stimulation, rats were allowed to consume saccharin and received a saline injection after the session. Suppression of saccharin consumption during electrical stimulation was learned within 12 trials. Rats trained in the reverse discrimination, i.e., sessions with no electrical stimulation paired with LiCl injection, showed a similar learning curve. Animals injected prior to the session with the hallucinogenic 5-HT_2 agonist (±)-DOI associated DOI with electrical stimulation of the dorsal raphe nucleus. Thus, animals may be trained to discriminate electrical stimulation of the dorsal raphe nucleus. Furthermore, animals generalize from activation of 5-HT_2 receptors to electrical stimulation of the dorsal raphe nucleus.

Electrical stimulation Dorsal raphe nucleus DOI 5-HT_2 agonist 5-Hydroxytryptamine Discrimination Rats

CURRENT hypotheses for the actions of indolealkylamine and phenylalkylamine hallucinogens suggest an interaction with 5-hydroxytryptamine (5-HT) systems of the brain. Data supporting this hypothesis are a) binding of hallucinogenic drugs to 5-HT receptors particularly the 5-HT_2 subtype (14, 17,22,28,33), and b) antagonism of the behavioral effects of these hallucinogenic drugs with antagonists such as ketanserin and pirenpirone which are selective for the 5-HT_2 receptors (16,26,27,32,33,40).

The dorsal raphe nucleus of the midbrain is one of the major nuclei of 5-hydroxytryptamine (5-HT) cells that project to the forebrain. Electrical stimulation of the dorsal raphe nucleus (DRN) activates ascending 5-hydroxytryptamine (5-HT) neurons. This stimulation has been shown to increase the tissue levels of the 5-HT metabolite 5-HIAA (1,20), increase the turnover of 5-HT in forebrain regions (9,35,37), and increase the levels of extracellular 5-HT as determined by in vivo microdialysis (36).

Animals can be trained to discriminate electrical stimulation of the DRN. Using a classical operant drug discrimination paradigm, Hirschhorn et al. (18) trained rats to discriminate nonaversive stimulation of the DRN. Animals were trained to a stimulus of 200–300 μA biphasic stimulation. After learning this discrimination, rats were tested for generalization to LSD or morphine. Rats generalized from the hallucinogen LSD (100 μg/kg) to electrical stimulation of the DRN.

The purpose of this investigation was to further examine the discrimination of DRN stimulation and to extend these results to the 5-HT_2 agonist DOI. DOI is an agonist at 5-HT_2 receptor (2,8,10,12,13,22,31,40,41). DOI binds to 5-HT_{2A} and 5-HT_{2C} receptors in the forebrain, produces behavioral effects that are blocked by the 5-HT_{2A} antagonist ketanserin, and

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acts in a manner similar to 5-HT to stimulate phosphoinositol hydrolysis in forebrain regions, an action of 5-HT attributed to activation of 5-HT_{2A} receptors.

An inherent problem with training animals to discriminate electrical stimulation using classical operant behavioral techniques is the time required for training may be long enough to produce tissue changes around the electrode, thus reducing the efficacy of the stimulation. To facilitate learning of the stimulus cue, a rapid method of discrimination training using a conditioned taste aversion paradigm was utilized (19,21).

METHOD

Male Sprague-Dawley rats (250–300 g, Charles River Laboratories, Wilmington, MA) were trained to drink a 0.25% saccharin solution in daily 30-min sessions. Animals were water deprived for 22 h prior to the session. Animals were given access to water for 1 h after the end of the session, as well as continuous access to food. Once stable levels of saccharin were being consumed, daily sessions were reduced to 15 min. Animals were then implanted with stainless steel bipolar electrodes (Plastics One, Roanoke, VA) into the DRN at the stereotaxic coordinates of A 1.2; L 0.0; V 3.5, with reference to intraural zero according to the atlas of Paxinos and Watson (29). Anesthesia was induced by pentobarbital sodium (50 mg/kg, Sigma Chemical) and supplemented with additional pentobarbital sodium or halothane as needed.

Electrical stimulation (ES; 100 μA, 100 μs biphasic pulse pairs at 20 Hz) was delivered on alternate days using a Grass S11 Stimulator with Grass Constant Current Stimulus Isolation Units (Grass Instruments, Quincy, MA). Animals were placed in a standard Plexiglas animal cage without bedding. An electrode lead was attached to the electrode while the animal was under gentle hand restraint. The electrode lead was attached to a single channel commutator (both from Plastics One, Roanoke, VA) mounted on a Plexiglas cover for the cage. The animal was given access for 15 min to a 100 ml graduated drinking tube containing saccharin and the number of ml drank during the session recorded. In the first group of animals, electrical stimulation of the DRN was followed by an injection of 1 ml/kg LiCl (1.8 mEq/ml, 76.32 mg/ml, Sigma Chemicals) immediately after the session. This dose of LiCl makes the rat sick for approximately 1–2 min. The animals show a characteristic behavior that includes licking the sight of injection, hindlimb extension, and dorsiflexion. After injection, animals were placed back in their home cages and returned to the animal quarters. On nonstimulation days, the animals were connected to the electrode lead and placed in the cage without stimulation. Immediately after the session, the animals were injected with 1 ml/kg 0.9% NaCl. In the second group of animals, electrical stimulation of the DRN was followed by an injection of 0.9% NaCl, whereas nonstimulation was followed by an injection of LiCl. Thus, half of the animals were trained to associate electrical stimulation with LiCl injection, whereas the other half learned to associate nonstimulation with LiCl injection. The amount of saccharin consumed in milliliters was measured after each session.

For generalization testing, animals were injected IP with (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane HCl (DOI HCl, D101, Research Biochemicals, Inc., Nadick, MA) or saline 5 min prior to the beginning of the session. DOI was dissolved in distilled water. Animals were then allowed access to a saccharin solution for 15 min. No stimulation was administered nor were any injections given after the session.

In order to determine if DOI alone had an effect on the consumption of saccharin, a separate group of 10 animals was trained to drink saccharin. These animals were deprived of access to water in their home cages in the same manner described above. DOI (0.25, 0.5, and 1.0 mg/kg) was administered 5 min before the beginning of the session. Saccharin was then offered to the animals for 15 min and the amount of saccharin (ml) consumed was recorded.

After the behavioral testing was complete, animals were anesthetized with an overdose of Na pentobarbital. After the animal had reached a surgical level of anesthesia, the animal was decapitated and the brain removed and frozen. The brain was then mounted on a freezing stage microtome and sliced to determine electrode placement.

Data was analyzed as the amount of saccharin consumed during the test session. A two-way analysis of variance with repeated measures was used to compare stimulation vs. nonstimulation during training. A one-way analysis of variance with repeated measures was used to examine the effects of DOI. A Student-Newman-Keuls test was used for post hoc comparisons. A probability of less than 5% was used in all tests. Statistics were performed using SigmaStat v.1.01 (Jandel Scientific, San Rafael, CA).

RESULTS

Animals learned to drink a steady level of saccharin within 12 sessions with consumption of 18.3 ± 1.0 ml of saccharin in 30 min. On the first day of 15 min sessions, animals consumed 19.2 ± 0.6 ml Stimulation of the DRN prior to the beginning of discrimination training decreased saccharin consumption, but by four exposures the animals were drinking equivalent amounts on stimulated and nonstimulated days (12.4 ± 1.2 ml and 14.6 ± 1.0 ml, respectively).

Pairing of the stimulation or nonstimulation of the DRN with LiCl produced a clear discrimination in 6 reversals or 12 sessions (Fig. 1). Pairing of stimulation with LiCl injection resulted in a significant effect on stimulation [stimulation vs.

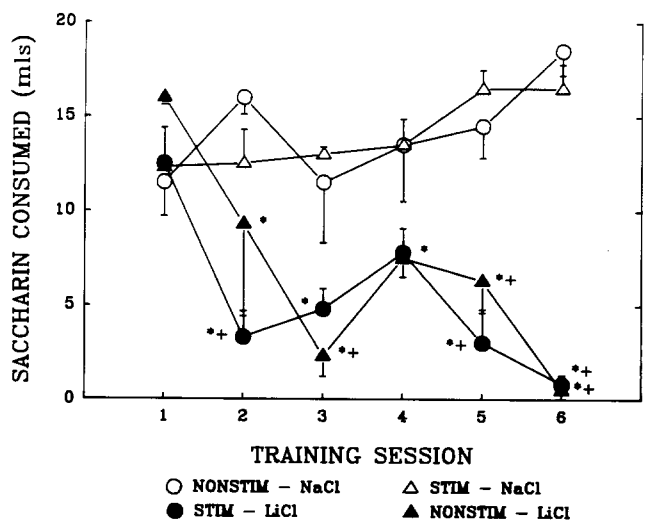

FIG. 1. The training curves for discrimination of ES of the DRN. Graph shows two groups trained under two conditions. One group was trained with ES associated with LiCl injection (circles). The other group was trained with nonstimulation associated with LiCl injection (triangles). Points represent mean ± SEM, $n = 4$. *Significantly different from session 1; +Significantly different from corresponding NaCl session, two-way ANOVA, Student-Newman-Keuls post hoc test, $p < 0.05$.

nonstimulation, $F(1, 15) = 22.685$] and the interaction between session number and stimulation, $F(5, 15) = 5.608$, without a significant effect on session number, $F(5, 15) = 2.039$. Pairing of nonstimulation with LiCl injection resulted in a significant effect of stimulation, $F(1, 15) = 29.251$, session, $F(5, 15) = 7.701$, and the interaction between stimulation and session, $F(5, 15) = 6.99$. No differences were seen between animals with stimulation of the DRN paired with LiCl and nonstimulation paired with LiCl (Fig. 1). Thus, stimulation of the DRN alone does not affect the animal's ability to drink saccharin or to associate LiCl with stimulation.

In order to determine the effects of lower levels of stimulation, the current was lowered to 20 μA. Under this condition, animals with stimulation associated with LiCl drank 11.3 ± 2.2 ml during stimulation (data not shown). Likewise, rats with nonstimulation associated with LiCl drank 9.25 ± 1.3 ml saccharin during stimulation. These data suggest that animals do not generalize completely from stimulation at 100 μA to stimulation at 20 μA.

Injection of the hallucinogenic 5-HT_2 agonist DOI before the session resulted in stimulation appropriate behavior (Fig. 2). Animals that had been conditioned to suppress saccharin consumption during stimulation showed a suppression of saccharin drinking, $F(3, 9) = 88.47$, with generalization occurring at all doses of DOI. Animals conditioned to suppress saccharin consumption during nonstimulation also showed stimulation appropriate responding at doses of 0.1 and 0.5 mg/kg DOI, $F(3, 9 = 28.203$. At a dose of 1.0 mg/kg DOI, both groups showed a suppression of drinking, suggesting that at this dose DOI suppresses behavior (Fig. 2). Thus, DOI generalizes to stimulation of the DRN in this paradigm.

In a separate experiment, rats drinking saccharin without training in the discrimination paradigm showed a significant decrease in saccharin consumption after 1.0 mg/kg DOI, but not 0.25 or 0.5 mg/kg (data not shown).

DISCUSSION

Male Sprague-Dawley rats were trained to discriminate electrical stimulation of the dorsal raphe nucleus using a discriminated taste aversion paradigm. The training time in the current study was similar to the rapid training of drug discrimination using this paradigm reported by Lucki (21) and Riley and co-workers (24,34). Hirschhorn et al. (18), obtained the same discrimination using a classical operant paradigm with higher stimulus intensity. The discriminated taste aversion paradigm allows for rapid training of animals as compared to a classical two-lever operant paradigm which requires more than twice as many sessions to reach a minimal discrimination [Mokler, unpublished data; (18)].

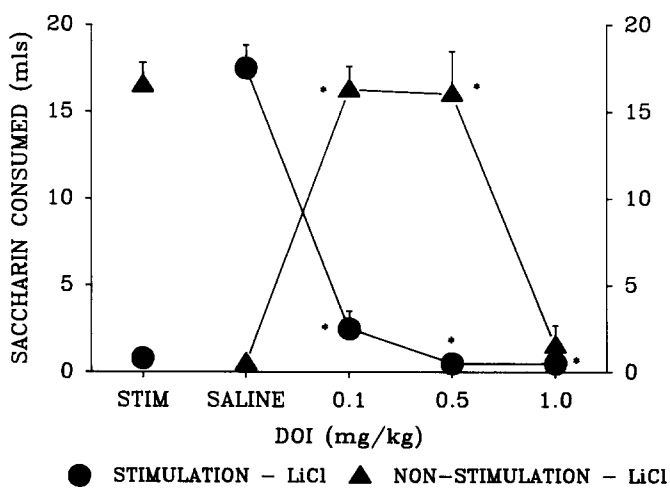

FIG. 2. Effects of administration of DOI, IP before the session in rats trained to discriminate ES of the DRN. Animals were trained to associate ES with injection of LiCl (circles) or NaCl (triangles). Points represent mean ± SEM, $n = 4$. *Significantly different from saline. One-way ANOVA, Student-Newman-Keuls post hoc test, $p < 0.05$.

A reversal of the discrimination conditions was used to determine the effects of electrical stimulation of the dorsal raphe nucleus on the ability of the animals to perform the behavioral task. One group was trained to suppress drinking of saccharin during ES and the other to suppress drinking during nonstimulation sessions. The two conditions yielded almost identical results, indicating that the electrical stimulation did not influence the ability of the animals to perform the behavior or, indeed, to acquire the discrimination. Thus, it is the aversive conditions the rats associated with stimulation of the DRN that affected saccharin drinking behavior, not the ES itself.

The hallucinogenic 5-HT_2 agonist DOI generalized to ES of the DRN. Following DOI administration, animals trained to suppress saccharin consumption during electrical stimulation suppressed saccharin consumption. Conversely, animals trained to drink saccharin under ES continued to drink at normal levels with DOI administration. At the highest dose of DOI, saccharin consumption was suppressed in both groups. This, and independent findings that 1.0 mg/kg DOI suppresses saccharin consumption, indicates that this dose suppresses behavior generally. DOI has been shown to suppress milk consumption at a dose of 1 μmol/kg (.36 mg/kg) (38). In the present study, doses of .25 or .5 mg/kg DOI did not suppress saccharin consumption. The differences between the results of Simansky and Vaidya (38) and our results may relate to the state of deprivation of the animals.

The present results also suggest that activation of ascending 5-HT neurons of the dorsal raphe nucleus may have stimulus properties similar to activation of 5-HT_2 receptors. This is similar to the findings of Hirschhorn et al. (18) that LSD also generalizes to electrical stimulation of the DRN. In a number of behavioral and neurochemical experiments LSD has been shown to interact with 5-HT_2 receptors (4–6,11,14,15,25,27, 30,40). This adds to considerable data to suggest that the hallucinogens act to stimulate postsynaptic receptors. Presumably the 5-HT_2 receptor plays a major role in these actions. Also of interest in this regard is the findings that projections of the DRN terminate in forebrain regions rich in 5-HT_2 receptors (3,23). Thus, stimulation of the DRN may preferential stimulate 5-HT_2 receptors.

Using a two-lever operant discrimination task, Glennon (13) showed that rats could be trained to discriminate DOI from saline. LSD and DOM, but not the 5-HT_{1A} agonists 8-OHDPAT or TFMPP, generalized to the stimulus properties of DOI. The present data suggests that activation of 5-HT_2 receptors with DOI has discriminative stimulus properties similar to the electrical stimulation of the DRN.

Numerous studies have shown that electrical stimulation of the DRN increases the release of 5-HT in forebrain regions (1,7,9,20,35–37). Recently, however, other studies have shown that the administration of DOI produces a decreased release of 5-HT in forebrain regions (41). Wright et al. (1990) further showed that microinjection of DOI into the frontal cortex did not produce a decrease in release of 5-HT as determined by in vivo microdialysis. This suggests that DOI may produce

changes in the release of 5-HT in forebrain regions independent of, or secondary to stimulation of postsynaptic 5-HT_2 receptors.

Lower levels of ES of the DRN should serve as discrimination cues. Although Hirschhorn et al. (18) used higher levels of stimulation (200–300 μA) than in the current study, Wheeling et al. (39) have determined that the threshold of stimulus is lower than the levels employed in this work (20–30 μA). Data using a stimulation current of 20 μA, however, suggest this level of stimulation is not similar to the effects of stimulation at 100 μA. Further experiments are necessary to determine if animals can be trained to lower levels of stimulation.

These experiments have suggested a similarity between stimulation of one of the major nuclei of 5-HT cells projecting to the forebrain and the stimulus properties of a drug that stimulates postsynaptic 5-HT_2 receptors. These are preliminary findings that suggest a number of experiments to further explore the relationship between the hallucinogens and stimulation of the dorsal raphe nucleus.

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