Pharmacology Biochemistry and Behavior, Vol. 43, pp. 255–261, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Role of Locus Coeruleus and Serotonergic Drug Actions on Schedule-Induced Polydipsia

C. C. LU,* C. J. TSENG,* F. J. WAN,* T. H. YIN† AND C. S. TUNG†[1]

*Department of *Pharmacology and †Physiology,*
National Defense Medical Center, Taipei, Taiwan, Republic of China

Received 31 January 1992

LU, C. C., C. J. TSENG, F. J. WAN, T. H. YIN AND C. S. TUNG. *Role of locus coeruleus and serotonergic drug actions on schedule-induced polydipsia.* PHARMACOL BIOCHEM BEHAV **43**(1) 255–261, 1992.—Schedule-induced polydipsia (SIP) poses a general buffering property to reduce the heightened arousal produced by a schedule of intermittent feeding. It thus provides a unique opportunity to study CNS integration in stress-coping reactions. In the present study, we examined the role of the locus coeruleus (LC) and the pharmacological actions of serotonergic (5-HT_2) analogs on SIP. Water intake, licking, and bar presses per minute in rats were recorded as indices of SIP activity after they had been subjected to 1-h performance of a fixed-interval 1-min operant pellet conditioning. Our results showed that SIP was progressively decreased after lesions were placed bilaterally in the LC areas and then followed by further lesioning in the bilateral ventral tegmental area. Neurotoxin DSP-4 also had an inhibitory action on the SIP potency. In addition, SIP was attenuated by 2,5-dimethoxy-4-iodoamphetamine (0.1, 0.5, or 1.0 mg/kg, IP), a 5-HT_2 agonist, and activated by ritanserin (2.5 mg/kg, IP), a 5-HT_2 antagonist. After bilateral LC lesions, SIP was attenuated and the activating effect of RIT was abolished. Our data suggest that the LC is involved in the central integration of SIP and that the modulating effects of 5-HT_2 receptors on SIP depend upon the integrity of LC function.

Schedule-induced polydipsia Stress coping Locus coeruleus Ventral tegmental area Serotonergic analogs

PERIODIC schedules of pellet presentation elicit schedule-induced polydipsia (SIP), which shows a burst of vigorous drinking following almost every pellet delivery. This behavior is one kind of adjunctive behavior (8). Although a number of hypotheses have been advanced, our understanding of the nature of the SIP phenomenon remains inadequate in terms of both motivated learning and homeostatic drinking (7,14,19).

To elucidate the mechanisms of SIP, a number of studies have been directed toward finding anatomic and biochemical substrates that might be involved in development of this behavior. Emphasis has been focused on the central catecholaminergic systems. Robbins and Koob (22) reported a decade ago that initiation of SIP is dependent upon the mesolimbic dopaminergic system, specifically the ascending projections arising from the ventral tegmental area (VTA). Others also have reported that *d*-amphetamine administration facilitated the development of SIP (15). Selective lesions of the nucleus accumbens blocked the development of SIP, but selective lesions of the lateral septum had the opposite effect (26). Selective lesions of the medial prefrontal cortex, however, have failed to affect SIP (4). It is also known that VTA descending pathways innervate several brainstem regions, notably the locus coeruleus (LC) (13). The relationship of VTA–LC interactions to behavior regulation (1), such as in the control of SIP (10), is still an unsolved problem.

The LC is a bilateral pontine structure with a widespread terminal network throughout the neuraxis, which in primates accounts for about 70% of brain norepinephrine (NE). The activation of LC neurons in animals is known to be correlated with vigilance or arousal, particularly responses associated with noxious stimuli (25,27). A substantial binding and high levels of serotonin [5-hydroxytryptamine (5-HT)] have been found around LC regions (12). This indicates that LC receives 5-HT innervations, where an essential interaction between these two systems might be also required for animals in behavior regulation.

Electrophysiological evidence indicates that 5-HT might have an inhibitory influence on the discharge of LC neurons (23), and this regulation appears to be mediated at an extracoerulear 5-HT_2 receptor (20). Although recent findings have criticized that 5-HT has a pronounced and consistent effect on basal LC discharge, this agent still potently and selectively

[1] Requests for reprints should be addressed to Che-Se Tung, M.D., Ph.D., Department of Physiology, National Defense Medical Center, P.O. Box 90048-503, Taipei, Taiwan, Republic of China.

attenuates responses of LC neurons to some excitatory stimuli in anesthetized rats (2). For many years, serotonergic systems have been implicated in the processes of underlying anxiety (9) and depression, and a great deal of research has been devoted to these topics. It has been found that 5-HT_2 antagonists have effects on reinforcement rate at schedules of regularly spaced intervals (17). Several NE reuptake blockers such as desipramine have effects similar to those of 5-HT_2 antagonists (11).

Based upon the above evidence, we were intrigued to explore the role of LC in SIP control. Actions of the 5-HT_2 receptor in modulating LC activity in arousal, which might be expressed by changes in SIP, is another interesting question we wished to address. Our purpose in the present study was to determine the influence of LC destruction on SIP maintenance. In addition, an ancillary topic was undertaken to determine the pharmacological effect of selective 5-HT_2 stimulation and antagonism on SIP activities.

METHOD

Animals

Male Sprague-Dawley rats weighing 300 ± 50 g were used. Rats were maintained on a 12 L : 12 D cycle (light at 7:00 a.m., off at 7:00 p.m.) at room temperature (25°C) and allowed access to food and water ad lib except during periods of controlled deprivation and experimentation. Rats were allowed to adjust to their home cages for at least 1 week before studies.

Behavioral Procedure

Apparatus. Four rodent operant chambers (Coulbourn Instruments, Lehigh Valley, PA) with matching sound attenua-

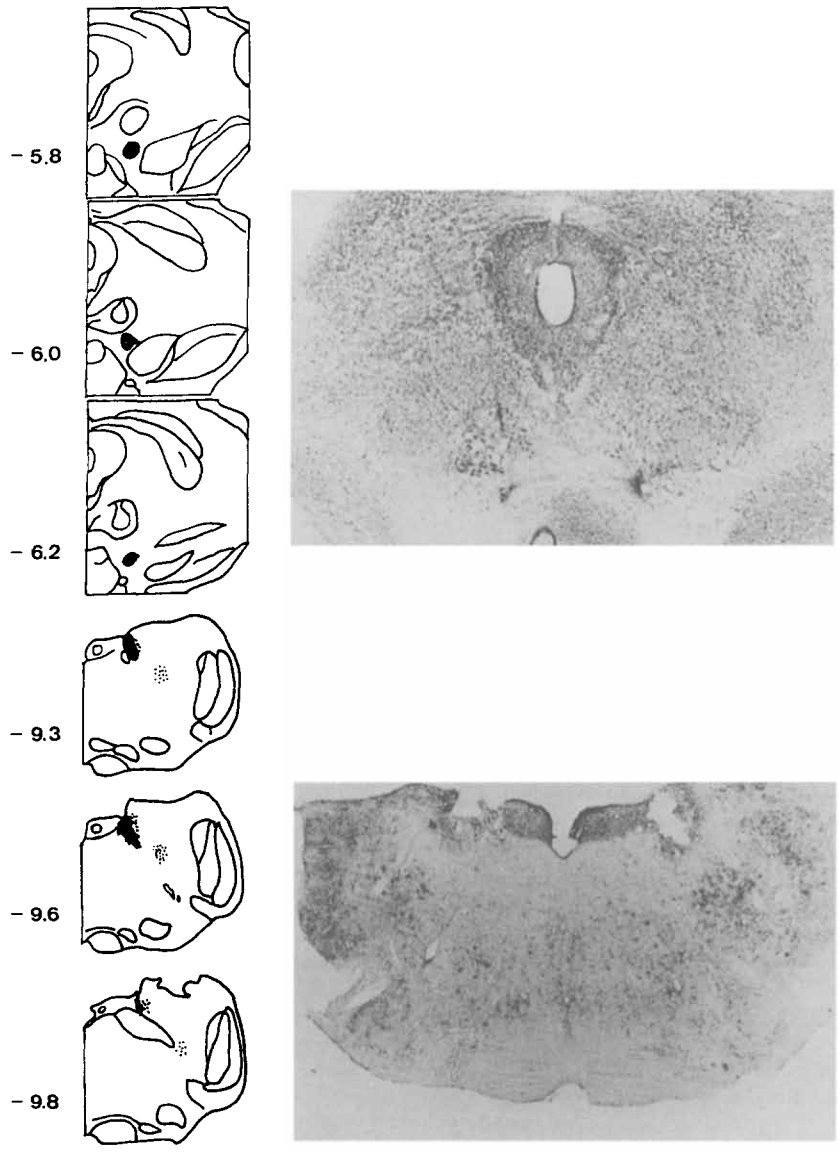

FIG. 1. Representation of size and location of bilateral symmetrical lesions (shaded areas) in the VTA (top) or LC (bottom). Numbers to the left of each section refer to AP coordinates according to Paxinos and Watson (18).

tion cubicles and 45-mg food pellet dispensers were used for SIP training. A 100-ml glass graduated cylinder was fixed on the back wall outside the chamber with its stainless steel spout protruding 2 cm into the chamber and 4 cm above the grid floor. The lever for pellet release was positioned on the wall 3 cm above the floor adjacent to a food chute and to the right of the water spout.

SIP training procedure. Rats were gradually reduced to 80% of their ad lib feeding weights by restricting their daily food rations for 1 week. The next 4 days, rats were trained in the operant chamber to press a lever for food pellets on a continuous food-reinforced schedule 1 h per day. On the fifth day, the schedule was changed to a session of 1 h per day on a fixed interval of 1-min food-reinforced schedule until SIP was fully developed. When SIP was developed and stabilized about 10 days later, we started the behavioral test. Number of licks and presses were recorded by individual counters, and water consumption was acquired by weighing the water bottle before and after the test.

Water deprivation procedure. Rats (n = 15) were deprived of water for 72 h before performing the drinking test. Thirst-induced drinking was evaluated by the total water intake immediately after water bottles were offered. Amount of water consumption was determined at 0.5, 1.0, and 2.0 h after drinking. These data were then utilized to compare between "adjunctive" and "deficit" drinking.

Stereotaxic surgery. After anesthesia with IP pentobarbital (40 mg/kg), rats were placed in a David Kopf (Tujunga, CA) stereotaxic apparatus and the incisor bar was adjusted until the heights of lambda and bregma skull points were equal. To destroy the targeted nucleus, bilateral lesions were made by radiofrequency-thermal electrode of 250 μm o.d. insulated except at the tip. This electrode was activated by passing a 20-V, 15-mA current for 60 s with a lesion temperature of 55°C at the tip (RFG-4A, Radionics, Randolph, MA). Sham lesions were made by placing the electrode in the brain 1 mm above the lesion loci but without passing current. The coordinates for lesions were (in mm): LC lesion, lambda −1.1, lateral ±1.0, ventral 6.0 from dura; VTA lesion, lambda +3.3, lateral ±0.65, ventral 7.5 from dura.

Initially, rats were received either LC or sham lesions; subsequently, 20 days later, they received VTA lesions. After surgery, rats were allowed 3 days to recover from surgery before the test. At the end of each experiment, rats were deeply anesthetized and perfused transcardially with 4% formalin. Whole brain was removed, cut in 40-μm frozen sections, and stained with cresyl violet for histological examination. The identification of lesion loci was based upon the coronal sections from Paxinos and Watson (18) as templates.

DSP-4 treatment and drug studies. Two divisions of SIP rats were tested by DSP-4 administration. In the first division, SIP rats were subdivided into three groups and tested by peripheral (IP) administration of DSP-4. Group 1 (n = 7) received 0.9% NaCl as control; the other two groups (n = 5 each) were administered a dose of DSP-4 (50 mg/kg) in equal volume as saline (0.1 ml). In the second division, again three groups of SIP rats were tested by central (ICV) administration of DSP-4 plus zimelidine. Group 1 (n = 5) received Ringer's solution as control; the other two groups (Group 2, n = 5; Group 3, n = 4) were administered a dose of zimelidine (2 mg/kg) 10 min before administration of DSP-4 (3 mg/kg) in equal volume as Ringer's solution (10 μl). Behavioral tests were always conducted 3 days after drug treatment. At the completion of the test on the 8th (Group 2) or 15th day (Group 3), animals in each group were killed by decapitation. The brain and heart were rapidly removed and chilled on an ice-cold plate. Several brain regions and the left ventricular muscle were dissected for NE and 5-HT assaying by the high-performance liquid chromatography with electrochemical detection (HPLC-ED) technique (6).

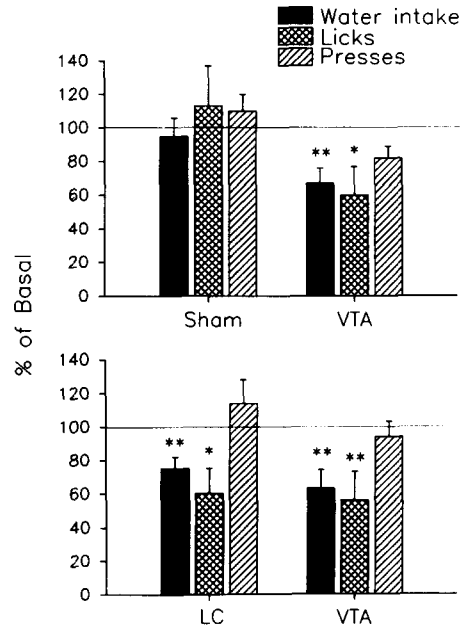

FIG. 2. Relative levels (%) of water intake, licks, and bar presses as compared to basal values before and after LC lesions and later superimposed by VTA lesions in SIP rats. Top: LC sham control (n = 11) followed by VTA lesions (n = 8). Bottom: LC lesions (n = 11) followed by VTA lesions (n = 7). Data indicated levels of SIP activity after 2 weeks of surgery. Values are mean ± SEM. $*p < 0.05$; $**p < 0.01$.

For drugs studies, SIP rats (n = 27) were injected IP 5 min before the test with either one dose of 5-HT_2 analog or vehicle (0.9% NaCl) in a total volume of 0.1 ml. These analogs were ritanserin (RIT), a 5-HT_2 antagonist, in a dosage of 2.5 mg/kg and 2,5-dimethoxy-4-iodoamphetamine (DOI), a 5-

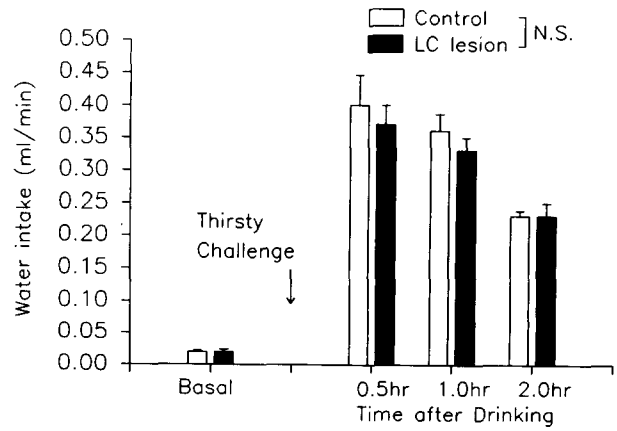

FIG. 3. Differences in water intake betwen sham control (n = 7) and LC lesion (n = 8) in water-deprived rats after 0.5, 1, and 2 h. Basal: normal rats' water intake in home cages. Values are mean ± SEM; N.S., nonsignificant.

TABLE 1

EFFECTS OF DSP-4 (50 mg/kg) OR CONTROL SALINE (100 μl) IP ADMINISTRATION ON ENDOGENOUS NE

Tissue (ng/mg)	Treatment		
	Control	1 Week	2 Week
Pfc	0.34 ± 0.07 (6)	0.18* ± 0.04 (5)	0.11* ± 0.03 (5)
Cx	0.18 ± 0.03 (7)	0.00* ± 0.00 (5)	0.01* ± 0.00 (5)
Hi	0.36 ± 0.06 (7)	0.00* ± 0.00 (4)	0.00* ± 0.00 (5)
Lm	0.45 ± 0.13 (6)	0.25 ± 0.01 (4)	0.13† ± 0.02 (4)
Hp	1.51 ± 0.38 (7)	1.04 ± 0.29 (5)	1.28 ± 0.47 (5)
P	1.14 ± 0.19 (7)	0.52* ± 0.09 (5)	0.25* ± 0.06 (5)
Lv	0.71 ± 0.14 (6)	0.60 ± 0.28 (5)	0.54 ± 0.07 (5)

Pfc, prefrontal cortex; Cx, cortex; Hi, hippocampus; Lm, limbic areas; Hp, hypothalamus; P, pons; Lv, left ventricle. Values are mean ± SEM (n = number of samples).

*$p < 0.01$.

†$p < 0.05$.

HT_2 agonist, in a dosage of 0.1, 0.5, or 1.0 mg/kg (Research Biochemical Inc., Wayland, MA).

Statistics

Changes of levels of water intake, licks, and bar presses were presented. Because of the differences between groups and individual animals during SIP analysis, basal values averaged from the last three sessions (−3 to 0 day) in each animal before surgical lesions were compared with the respective average value of sessions 13, 14, and 15 (2 weeks) after surgical lesions. Basal values averaged from the last three sessions (−3 to 0) in each animal before DSP-4 treatment were compared with the average value of 6, 7, and 8 sessions (Group 2) or 13, 14, and 15 sessions (Group 3). These changes were then shown by percentage (%) changes. In addition, basal values averaged from the last three sessions in each animal before 5-HT_2 analog treatment were compared with the individual values of the drug test. These changes were then shown by a mean value per minute of session records. Data were reported as mean ± SEM and were analyzed by Student's paired t-test. A two-tailed p-value less than 0.05 was selected as the lower limit for statistical significance.

RESULTS

Effects of Focal Brain Lesions on SIP

A total of 22 rats were used to test for the role of LC in SIP control. Rats were assigned to two groups according to the experimental protocol based upon lesion loci and the extent of tissue damage. In the first group, 11 rats received bilateral symmetrical lesions in both LC and VTA. In this group, we lost three rats due to failure to have subsequent lesions in VTA; therefore, only eight rats received a complete experimental protocol for both LC and VTA lesions. In the second group, another 11 rats received sham LC lesions and subsequent bilateral symmetrical VTA lesions. Again in this group, we lost four rats due to failure in the surgery of VTA lesions; therefore, only seven rats received a complete experimental protocol for both sham LC and VTA lesions. Histological examination revealed that all these lesions were located either at the LC or VTA area (Fig. 1).

Normal SIP rats under the 1-min FI food-reinforced schedule showed a steady high drinking action during the 1-h daily operant session (water intake: 25.8 ± 3.0 ml; licking: 6,050 ± 659 licks, n = 22), while with the sham-operated controls SIP rats decreased their activities in a persistent way after lesioning of the LC (water intake, $p < 0.01$; licks, $p < 0.01$) and VTA (water intake, $p < 0.01$; licks, $p < 0.05$) (Fig. 2).Sham LC lesions did not alter SIP activity but a significant fall occurred after bilateral VTA lesions (water intake, $p < 0.01$; licks, $p < 0.01$) (upper panel). No difference of bar presses between the trials before and after lesions was observed. The salient feature was that SIP activity after VTA lesions dropped to almost the same level as it had after LC lesions (lower panel).

Effects of LC Lesions on Thirsty Drinking

Normal rats (n = 8) in their home cages drank 28.8 ± 2.9 ml per day, and after bilateral LC lesions they still drank 26.4 ± 3.0 ml per day. When these rats were deprived of water for 72 h, a strong thirst is elicited as reflected by an immediate full-blown drinking when the water bottle is offered. Thirsty rats drank 27.6 ± 1.0 ml in 2 h, while after bilateral LC lesions they drank 27.0 ± 4.8 ml. There was no difference between those rats with or without LC lesions in total water consumption (Fig. 3).

Effects of DSP-4 on SIP

Two weeks after treatment, central as well as peripheral administration of DSP-4 did not result in depletion of NE in the left ventricular sympathetic fibers but did produce a severe and long-lasting depletion of NE in the coeruleo-NE brainstem projections (Table 1). We noted that 5-HT content was also slightly lowered by DSP-4 (50 mg/kg, IP) in some brain regions including the cortex, limbic areas, and pons; however, these were not statistically significant.

Figure 4 (upper panel) shows the action of DSP-4 (50 mg/kg, IP) on SIP activity. One week after DSP-4 treatment, the SIP activity, that is, licks and water intake, was significantly reduced (Group 2, n = 5) ($p < 0.01$) but this reduction was not seen 2 weeks later (Group 3, n = 5). On the other hand, central administration of DSP-4 (3 mg/kg) plus zimelidine (2

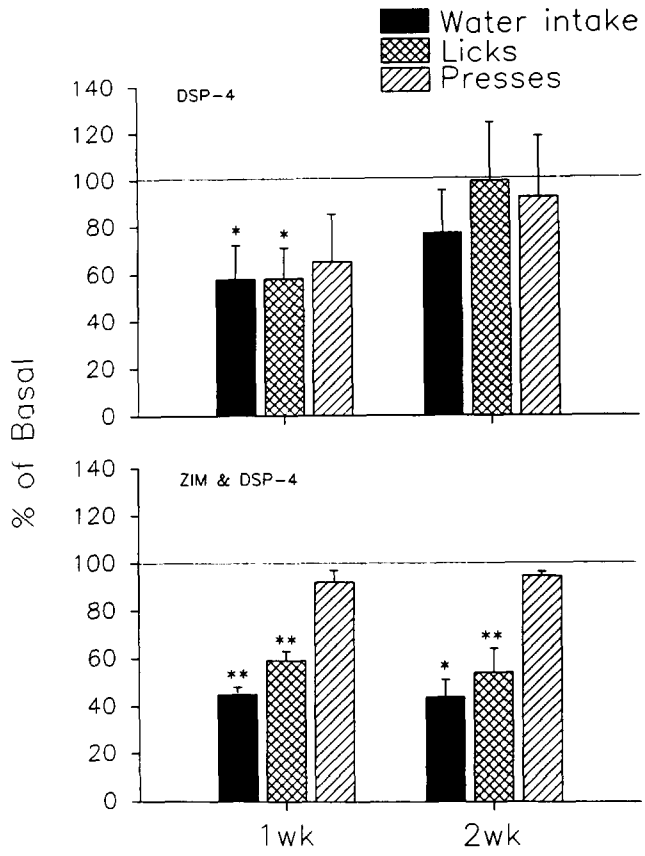

FIG. 4. Relative levels (%) of water intake, licks, and bar presses as compared to basal values after DSP-4 treatment in SIP rats. Data were averaged into plots for test days −3 to 0 (basal), 6–8 (1 week, Group 2), and 13–15 (2 weeks, Group 3). Top: DSP-4 (50 mg/kg) IP administration. Bottom: DSP-4 (3 mg/kg) plus zimelidine (2 mg/kg) ICV administration. Values are mean ± SEM. $*p < 0.05$; $**p < 0.01$.

mg/kg) still caused the similar reduction of SIP activity as the above treatment, and reduction extended to 2 weeks (Fig. 4, lower panel).

Effects of 5-HT Analogs on SIP

Figure 5 shows the vehicle or RIT effects on SIP activity. Under vehicle treatments, SIP rats ($n = 9$) drank water 22.0 ± 0.9 ml and licked 4,913 ± 463 during the 1-h session in performance. After administration of RIT at a dose of 2.5 mg/kg, rats exhibited a significant increase of SIP activities with changes in water intake (28 ± 2.1 ml/h, $p < 0.01$) and licks (7,284 ± 466/h, $p < 0.01$) but no changes in food pellet consumption or bar presses. After bilateral LC lesions, control SIP rats ($n = 10$) significantly ($p < 0.01$) decreased drinking (water intake: 15.1 ± 1.8 ml/h) and licking behaviors (3,719 ± 539 licks/h). The activation of RIT on SIP activity was entirely eliminated after bilateral LC lesions.

Finally, SIP activities were attenuated by DOI (0.1, 0.5, and 1.0 mg/kg). This was shown by the changes in water intake and licks in a dose-related manner ($n = 10$) (Fig. 6). RIT (2.5 mg/kg) significantly blocked DOI inhibition on water intake and licking and reversed the inhibitory action of DOI (0.5 mg/kg) on licking from a reduction to an increase ($p < 0.01$).

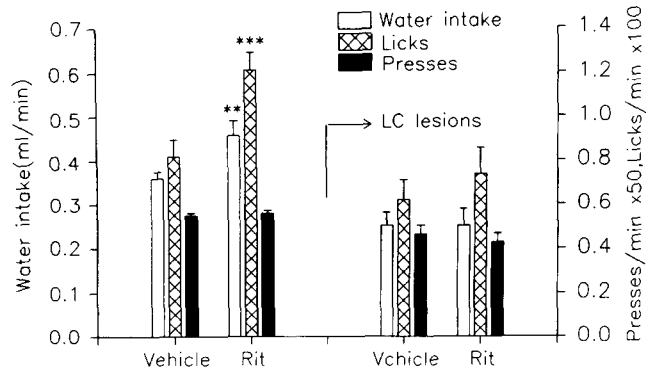

FIG. 5. Effects of RIT (2.5 mg/kg, IP) or vehicle (0.9% NaCl) on water intake, licks, and bar presses in SIP rats ($n = 17$). Values are mean ± SEM. $**p < 0.01$; $***p < 0.001$.

DISCUSSION

Because there exists a consistent relationship between pellet reward and drinking activation, SIP provides an interesting model for determining the neural basis of behavioral activations, for example, reinforcement and arousal (16). Previous findings have already indicated that SIP in the rat has a potent arousal-reducing property and reflects a mood buffering reaction (3). The propensity to exhibit SIP is related to the difference in coping capabilities among rats under various aversive stimulations (5). Wayner introduced a concept that a contingent reinforcing schedule will build up in rats a nonspecific motor excitability that is then released as adjunctive behavior (30). We also proposed in advance that when hungry rats are under an intermittent reinforced schedule they are aroused and stressed and are compelled to keep vigil to each reward event. Therefore, these rats build up internally a high tonic neural coupling activation between the CNS and the periphery

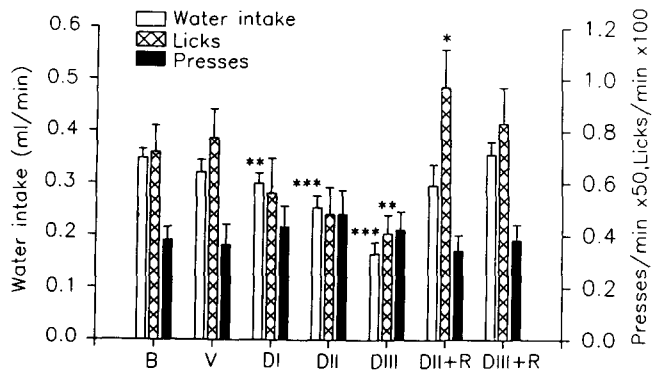

FIG. 6. Effects of 5-HT analogs on water intake, licks, and bar presses in SIP rats ($n = 10$). Data represent the averaged value from the last three sessions before treatment (B); value of vehicle treatment (V), values of DI–DIII (DOI 0.1, 0.5, or 1.0 mg/kg, IP) or DOI + RIT (R, 2.5 mg/kg, IP) treatments. Values are mean ± SEM. $*p < 0.05$; $**p < 0.01$, $***p < 0.001$.

(28,29), and then release externally in the form of SIP as a physical index of their stress coping reactions.

In studies in physiological behavior regulation, mesolimbic systems are recognized for incentive motivation or response initiation and are known to be important for behavioral vigor, for example, for the hungry rat to attain or perform SIP (15,22,26). On the other hand, the pontine nucleus LC and its ascending systems are recognized for their role in stimulus analysis and response selection and are known to be important for selective attention during stress, for example, for stressful rats to persevere a correct choice in a continuous performance task (24). To examine the interactions between these two systems and their specificity on SIP, we conducted the present studies by observing the behavioral changes after focal brain lesions or pharmacological challenges.

In the first experiment, we demonstrated that lesions in the LC are capable of attenuating SIP activities by lowering licks and water consumption (Fig. 2). Similar lowering effects also have been found in SIP rats after lesions in bilateral mesolimbic dopamine pathways at the level of the nucleus VTA (Fig. 2). Because these lesions did not affect the bar presses, we consider that SIP attenuation is not a result secondary to the action of motor disruption. Because thirsty rats after LC lesions did not show the lower drinking response observed in SIP rats (Fig. 3), we believe SIP attenuation is not caused by a disturbance of primary thirst either.

We thus speculate that lesions in the LC might incapacitate judgment of SIP rats to make proper postpellet drinking due to either distraction or primary deficit in attention. Because of this misjudgment, LC-lesioned rats lose their coping abilities in a stressful situation and consequently the SIP activities drop. On the other hand, the reduction of SIP after VTA lesions provided evidence that the VTA has an important function for the initiation and execution of motivated actions. This finding also extended the observations of many other investigators concerning dopaminergic terminal functions on SIP modulation. Furthermore, our data clearly show that the level of SIP potency is lowered persistently following both LC and VTA lesions. This implies that, if the rat is at well-established levels of SIP, the NE-containing pathways originating from the LC may facilitate the VTA-dopamine (DA) pathways. It also provided a possible explanation of why reward behavior under stress such as SIP is induced by the coping reactions due to LC activation. Whether LC or VTA lesions differ in terms of the postpellet temporal variation of SIP activity (21) is an interesting issue for future study.

From the biochemical approach, we found that the neurotoxin DSP-4 could deplete NE contents in the coeruleo-NE projections for at least 2 weeks (Table 1). Nevertheless, DSP-4 causes a partial reduction of the SIP activity within 1 week after it (50 mg/kg, IP) is given but then the activity returns to normal 2 weeks later (Fig. 4, upper panel). This phenomenon can be interpreted in two ways. First, LC systems may play an important role in SIP maintenance but NE projections from the LC may not be the only pathway involved in SIP regulation. Second, there are other neuronal circuits that can compensate for the loss of action consequent to LC lesions. Indeed, in this report we emphasized the influence of 5-HT on SIP integration. We also showed that depletion of the central coeruleo-NE projections but protection of the serotonergic pathways, achieved by an ICV injection of DSP-4 (3 mg/kg) plus zimelidine (2 mg/kg), could affect SIP similar to that after LC lesions (Fig. 4, lower panel).

Regarding the inhibitory effect of 5-HT on LC activities (2,18,22), we clearly demonstrated a dose-dependent suppression on SIP by DOI (Figs. 5 and 6), and these effects are reversed by RIT treatment. In addition, RIT caused a strongly enhanced SIP activity that is blocked by bilateral LC lesions. Because the properties of both compounds in behavioral modification are known to be mediated by selective 5-HT_2 receptors, our data thus are consistent with the findings that serotonergic influence on the LC are mediated via 5-HT_2 receptors. It furthermore implies that central raphe systems might link with the circuit of the LC and VTA to maintain this activated behavior.

Central catecholamines have been known to be involved in behavioral pathology of a number of neurological and psychiatric disorders. SIP may involve both DA and NE in behavior regulation. Our experimental findings suggested that the LC participates in the central integration of SIP. We also provided evidence that the central modulating effect of 5 HT_2 analogs on SIP depends upon the integrity of LC function.

ACKNOWLEDGEMENTS

This research was supported by NSC grant (79, 80-0412 BO16-110, 111) and a fellowship of the S. C. Wang foundation at National Defense Medical Center. C.C.L. and F.J.W. are postdoctoral fellows in NDMC. The authors thank Prof. C. Y. Chai for worthwhile discussions of this manuscript and N. Sy and W. Y. Lo for their technical assistance and preparation of this manuscript. This article was presented at the Society for Neuroscience 21st Annual Meeting, New Orleans, Louisiana, 1991.

REFERENCES

1. Antelman, S. M.; Caggiula, A. R. Norepinephrine-dopamine interactions and behavior. Science 195:646–653; 1977.
2. Aston-Jones, G.; Akaoka, G.; Charlety, P.; Chouvet, G. Serotonin selectively attenuates glutamate-evoked activation of noradrenergic locus coeruleus neurons. J. Neurosci. 11:760–769; 1991.
3. Brett, L.; Levine, S. The pituitary-adrenal response to "minimized" schedule-inducing drinking. Physiol. Behav. 26:153–158; 1981.
4. Christie, M. J.; Beart, P. M.; Louis, W. J.; Gibson, S. J.; Singer, G.; Papasava, M. 6-Hydroxydopamine and excitotoxin lesions of medial prefrontal cortex fail to affect schedule-induced drinking in the rat. Behav. Brain Res. 19:183–186; 1986.
5. Dantzer, R.; Terlouw, C.; Tazi, A.; Koolhaas, J. M.; Bohus, B.; Koob, G. F.; Le Moal, M. The propensity for schedule-induced polydipsia is related to differences in conditioned avoidance behavior and in defense reactions in a defeat test. Physiol. Behav. 43:269–273; 1988.
6. Donzanti, B. A.; Yamamoto, B. K. A rapid and simple HPLC microassay for biogenic amines in discrete brain regions. Pharmacol. Biochem. Behav. 30:759–799; 1987.
7. Falk, J. L. Conditions producing psychogenic polydipsia in animals. Ann. NY Acad. Sci. 157:569–589; 1969.
8. Falk, J. L. The nature and determinants of adjunctive behavior. Physiol. Behav. 6:577–588; 1971.
9. Iversen, S. D. 5-HT and anxiety. Neuropharmacology 23:1553–1560; 1984.
10. Lu, C. C.; Wan, F. J.; Tseng, C. J.; Yin, T. H.; Tung, C. S. Schedule-induced polydipsia enhances both mesolimbic dopaminergic and pontine noradrenergic activities in the rats. The Sixth Joint Annual Conference of Biomedical Sciences (Taipei, ROC). 1991: abstr. 138.

11. Marek, G. J.; Li, A. A.; Seiden, L. S. Selective 5-hydroxytryptamine$_2$ antagonists have antidepressant-like effects on differential-reinforcement-of-low-rate 72-second schedule. J. Pharmacol. Exp. Ther. 250:52-59; 1989.
12. McRae-Degueurce, A.; Milon, H. Serotonin and dopaminergic afferents to the rat locus coeruleus: Biochemical study after lesioning of the ventral mesencephalic tegmental-A 10 region and the raphe dorsalis. Brain Res. 263:344-347; 1983.
13. McRae-Degueurce, A.; Rosengren, L.; Haglid, K.; Augustsson, I.; Dahlstrom, A. Dopaminergic terminals in the rat locus coeruleus: An immunocytochemical investigation. Acta Physiol. Scand. 133:583-585; 1988.
14. Mittleman, G.; Brener, J.; Robbins, T. W. Physiological correlates of schedule-induced activities in rats. Am. J. Physiol. 259: R485-R491; 1990.
15. Mittleman, G.; Valenstein, E. S. Individual differences in non-regulatory ingestive behavior and catecholamine systems. Brain Res. 348:112-117; 1985.
16. Mittleman, G.; Whishaw, I. Q.; Jones, G. H.; Koch, M.; Robbins, T. W. Cortical, hippocampal, and strital mediation of schedule-induced behaviors. Behav. Neurosci. 104:399-409; 1990.
17. O'Donnell, J. M.; Seiden, L. S. Differential-reinforcement-of-low-rate 72-second schedule: Selective effects of antidepressant drugs. J. Pharmacol. Exp. Ther. 224:80-88; 1983.
18. Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. New York: Academic Press; 1982.
19. Porter, J. H. Schedule-induced polydipsia: Another look at water intake volume regulation. Physiol. Behav. 35:221-227; 1985.
20. Rasmussen, K.; Glennon, R. A.; Aghajanian, G. K. Phenethylamine hallucinogens in the locus coeruleus: Potency of action correlates with rank order of 5 HT$_2$ binding affinity. Eur. J. Pharmacol. 132:79-82; 1986.
21. Riley, A. L.; Schoening, G. A.; Wetherington, C. L. A software package for the microcomputer control and analysis of research on schedule-induced polydipsia. Physiol. Behav. 35:825-829; 1985.
22. Robbins, T. W.; Koob, G. F. Selective disruption of displacement behavior by lesions of the mesolimbic dopamine system. Nature 285:409-412; 1980.
23. Segal, M. Serotonergic innervation of the locus coeruleus from the dorsal raphe and its action on responses to noxious stimuli. J. Physiol. 286:401-415; 1979.
24. Selden, N. R. W.; Coel, B. J.; Everitt, B. J.; Robbins, T. W. Damage to ceruleo-cortical noradrenergic projections impairs locally cued but enhances spatially cued water maze acquisition. Behav. Brain Res. 39:29-51; 1990.
25. Svensson, T. H. Peripheral, autonomic regulation of locus coeruleus norepinephrine neurons in brain: Putative implications for psychiatry and psychopharmacology. Psychopharmacology (Berl.) 92:1-7; 1987.
26. Taghzouti, K.; Simon, H.; Tazi, A.; Dantzer, R.; Le Moal, M. The effect of 6-OHDA lesions of the lateral septum on schedule-induced polydipsia. Behav. Brain Res. 15:1-8; 1985.
27. Tung, C. S.; Ugedo, L.; Grenhoff, J.; Engberg, G.; Svensson, T. H. Peripheral induction of burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids. Synapse 4: 313-318; 1989.
28. Tung, C. S.; Yin, T. H. Clonidine suppression and its adrenoreceptor mediation in schedule-induced polydipsia. Physiol. Behav. 40:317-322; 1986.
29. Tung, C. S.; Yin, T. H.; Wayner, M. J.; Barone, F. C. Effects of subdiaphragmatic vagotomy on schedule induced drinking and schedule dependent lever pressing. Physiol. Behav. 25:745-751; 1980.
30. Wayner, M. J. Motor control functions of the lateral hypothalamus and adjunctive behavior. Physiol. Behav. 5:1319-1325; 1970.