REVISTA ESPAÑOLA DE FISIOLOGIA, 35, 219-228. 1979

Inhibition of the Activity of the Respiratory and Vasomotor Centers by Centrally Administered 5-Hydroxytryptamine in Cats

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(Received on September 8, 1978)

J. A. ARMIJO, A. MEDIAVILLA and J. FLOREZ. *Inhibition of the Activity of the Respiratory and Vasomotor Centers by Centrally Administered 5-Hydroxytryptamine in Cats.* Rev. esp. Fisiol., 35, 219-228. 1979.

The influence of 5-hydroxytryptamine (5-HT) on the activity of the respiratory and vasomotor centers was studied by injecting 5-HT into the lateral and fourth ventricles of lightly anaesthetized cats. 50 and 500 μg of 5-HT injected into the lateral ventricle induced a shortlasting increase in frequency and/or tidal volume followed by a prolonged and dose-dependent reduction of frequency, tidal volume and minute volume, concurrent with an increase in end expiratory CO_2. The CO_2 responsiveness of the respiratory center was depressed and the blood pressure levels were also lowered. All these effects were markedly enhanced by monoamine oxidase inhibition with i.v. tranylcypromine injected 75 min prior to 5-HT. 50 μg of 5-HT injected into the fourth ventricle induced a depression of respiration similar to that observed in the lateral ventricle studies, with the exception that the early stimulation was abolished.

Previous experiments showed that the increase in brain 5-hydroxytryptamine induced by administration of 5-HT precursors in cats, resulted in a depression of the respiratory and vasomotor centers which could be prevented by intracerebral injection of the l-aromatic aminoacid decarboxylase inhibitor Ro 4-4602 (6, 18). A suggestion was made that the increase in central serotonergic control might have an inhibitory influence upon the medullary centers. The direct injection of 5-HT into the cerebroventricular system has provided ambiguous results. FELDBERG and SHERWOOD (14) and GADDUM and VOGT (19) described that 5-HT injected into the lateral ventricles of awake cats induced tachypnea for about 30 minutes. On the other hand, BAUM and SHROPSHIRE (7) reported that intracerebroventricular 5-HT reduced the blood pressure and sympathetic nerve activity of anesthetized cats. The aim of the present study was to delineate in more detail the intensity of the effects of 5-HT on respiration and blood pressure in cats, and to ascertain

the time course and the central level of action. For this purpose the respiratory and blood pressure effects of 50 and 500 μg of 5-HT, administered as a bolus injection into the lateral and fourth ventricles of anesthetized cats, were followed for at least four hours under normal conditions and after monamine oxidase inhibition with tranylcypromine. The respiratory response to 5-HT was studied during resting conditions and under the influence of CO_2 challenge.

Materials and Methods

Experiments were performed in 56 cats of either sex, weighing from 2.5 to 3.5 kg. Injections into the lateral and fourth ventricle were made in 33 and 8 cats, respectively, anesthetized with a mixture of sodium pentobarbital (25 mg/kg) and urethane (500 mg/kg) i.p. After cannulation of the trachea, cranial screw type cannulae (David Kopf Instruments) were inserted stereotaxically into the anterior horn of the right lateral ventricle or into the fourth ventricle, following the coordinates of McCarthy and Borison (29). Five cats were decerebrated at the midcollicular level under temporary halothane anesthesia. Respiration was recorded by means of either a body plethysmograph or a pneumotachograph adapted to an integrator to yield the full respiration wave. Blood pressure was obtained from the right common carotid artery. End-expiratory CO_2 concentration was monitored by continuous sampling of tracheal air through a Godart Infant CO_2 infrared analyser. Respiration was assessed by measuring the spontaneous resting respiratory parameters as well as the respiratory response to stimulation with 5 % CO_2 in O_2 over a period of 5 min. In the anesthetized animals with intact brain, the experiment began 2 hr after the i.p. injection of anesthetics. In the decerebrate cats, halothane was discontinued as soon as the decerebration was completed; an interval of two hours elapsed between the interruption of the anesthetic and the start of the experiment. All experiments were initiated by obtaining control values of resting and CO_2-stimulated respiration.

In the time course studies, all values are expressed as the percent change referred to the control value, unless otherwise indicated. Symbols shown in figures are means of the percent changes $\pm$ standard error of the mean. Student's t test was used to determine the statistical significance of the differences between means.

Drugs. 5-hydroxytryptamine creatinine sulfate (Sigma) was diluted in artificial cerebrospinal fluid to the concentration of 50 and 500 μg in 100 μl for injections in the lateral ventricle, and in 50 μl for injections in the fourth ventricle. The solutions were buffered with sodium hydroxide to a pH of 7.4. Monoamine oxidase inhibition was accomplished with *dl*-tranylcypromine (Smith, Kline and French) at the dose of 5 mg/kg i.v. 5-HT was administered to MAO-inhibited cats 75 min after tranylcypromine injection.

Results

5-HT in the lateral and fourth ventricle of anesthetized cats. The spontaneous variation of the respiratory activity in the course of anesthesia was followed in a control group of 5 cats which received 100 μl of CSF solution in the right lateral ventricle. The most characteristic feature was the steady increase in respiratory frequency observed during the 4 hours of the experiment (fig. 1): it rose from a control value of 30.8 $\pm$ 2.2 (0 h) to a peak of 39.6 $\pm$ 5.2 (4 h) breaths per min. Since tidal volume was only minimally increased, changes in minute volume closely paralleled those of frequency, the values being increased from 906 $\pm$ 79.0 ml up to 1,202 $\pm$ 147.2 ml.

5-hydroxytryptamine was injected in the right lateral ventricle at the dose of

50 μg (11 cats) and 500 μg (5 cats). Fifty μg of 5-HT induced during the first 5 min a brief increase in tidal volume followed by a slight reduction, and a moderate but prolonged decline of frequency which reached the lowest value (—7.5 ± 1.7 %) 1 h after injection (fig. 1). After a short-lasting increase, minute volume was also reduced from 879.3 ± 82.5 ml down to 802.8 ± 84.4 ml at 60 min, and CO_2 levels were increased from 4.05 ± 0.24 to 4.35 ± 0.13 %. Subsequently these values were steadily recovered toward the baseline level. If independently considered, these changes may appear minimal; however, if the course of the respiratory effects induced by 50 μg of 5-HT is compared to that of the control group it becomes apparent that 5-HT

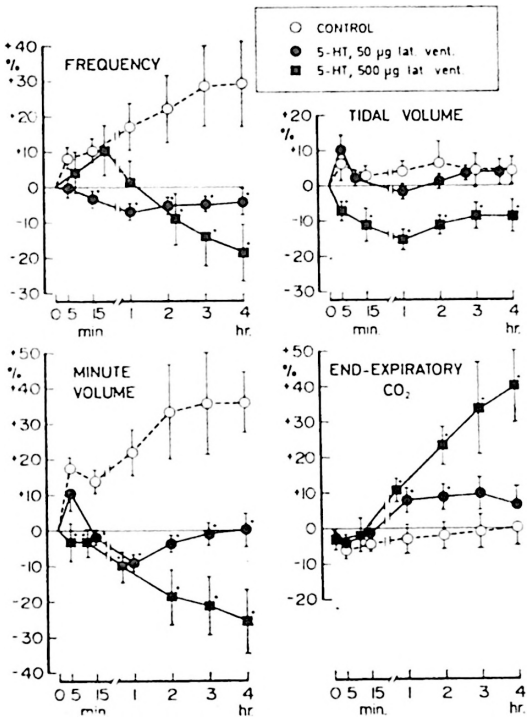

Fig. 1. *Time course of the respiratory parameters of anaesthetized cats receiving artificial CSF* (A, *n=5*), *5-HT 50 μg* (B, *n=11*) *and 5-HT 500 μg* (C, n=*5*) *in the lateral ventricle.*
Each symbol represents the mean ± S.E.M. of the percent change referred to the control (time 0) value. Asterisks indicate statistical significance ($p < 0.05$ or less) when values are compared to the control group. Actual values at time 0: Frequency (breaths per min), *A:* 30.8 ± 2.2, *B:* 37.7 ± 2.4, *C:* 31.8 ± 4.3; tidal volume (ml), *A:* 29.0 ± 1.0, *B:* 23.5 ± 1.7, *C:* 31.6 ± 2.5; minute volume (ml), *A:* 906.0 ± 79.0, *B:* 879.3 ± 82.5, *C:* 979.0 ± 105.5; end-expiratory CO_2 (vol. %), *A:* 4.6 ± 0.3, *B:* 4.05 ± 0.2, *C:* 4.1 ± 0.3.

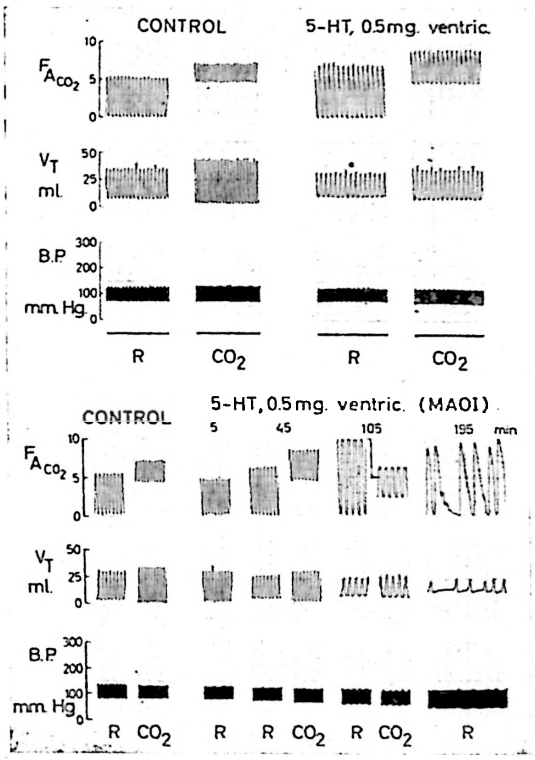

Fig. 2. *Effects of 5-HT injected into a lateral ventricle, on the resting respiration (R) and on the steady state response to the inhalation of a mixture of 5 % CO_2 in O_2 (CO_2), in a cat non-pretreated (upper half) and pretreated with a MAO inhibitor (lower half).* For each cat, from top to bottom, end-expiratory % CO_2, plethysmographic recording of respiration (inspiration upwards, V_T: tidal volume), and blood pressure.

depressed ventilation significantly, mostly accounted for by the influence on respiratory frequency. The depressant effect of 5-HT on respiration was enhanced at the dose of 500 μg; after eliciting an increase in frequency and reduction in amplitude for a period of about 45 min, this dose of 5-HT depressed frequency, tidal and minute volume, and increased end-expiratory CO_2 during the three subsequent hours (fig. 1); ventilation was reduced from 1,043 ± 93.1 to 744 ± 44.8 ml, and end-tidal CO_2 was elevated from 4.2 ± 0.3 up to 5.8 ± 0.5 %. CO_2-ventilation relationship curves were obtained at times of maximal depression (fig. 2 and 3). Both doses of 5-HT shifted to the right the relationship curves; 50 μg induced a small non-significant and parallel displacement, whereas 500 μg induced a significant shift and a reduction of the slope.

To obviate any suprapontine action of 5-HT, the amine was injected in the IV

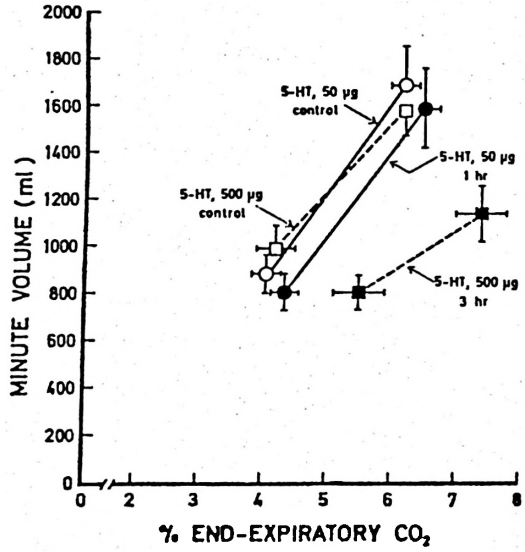

Fig. 3. *Effect of 5-HT on the steady-state relationships between end-expiratory CO_2 and minute ventilation, at time 0 (control) and 1 and 3 hr after injection of 50 and 500 µg of 5-HT, respectively.*

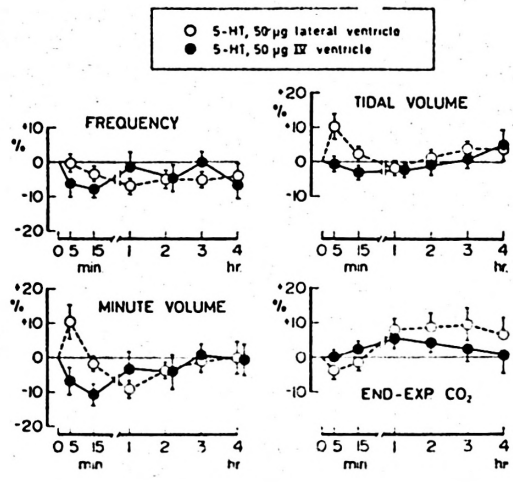

Fig. 4. *Time course of the respiratory effects induced by 5-HT injected into a lateral and fourth ventricle.*
Each symbol represents the mean ± S.E.M. of the percent change referred to the control value. Actual values at time 0: Lateral ventricle: *see* legend of fig. 1; fourth ventricle: frequency (breaths per min), 38.0±2.9; tidal volume (ml), 25.5±1.08; minute volume (ml), 976.4 ± 96.6; end-expiratory CO_2 (vol. %), 5.1 ± 0.24.

ventricle of 8 cats at the dose of 50 μg in 50 μl. The respiratory effects were similar to those induced by the same dose in the lateral ventricle (fig. 4), with the exception that the early stimulation of tidal and minute volume was eliminated; therefore ventilation was depressed from the time of injection.

5-HT in MAO-inhibited cats. Inhibition of monoamine oxidase was accomplished with tranylcypromine, Before studying the influence of the inhibitor on the respiratory response to 5-HT, the respiratory effects of the drug were investigated in two preparations: decerebrate-unanesthetized and intact anesthetized cats (n = 5 and 10, respectively). The time course of the effects was followed for 5 hr (fig. 5). Tranylcypromine induced in both preparation an immediate stim-

ulation of frequency, tidal volume, minute volume and sighing activity, which lasted for about 60 min in the anesthetized cats and 2 hr in the decerebrate animals (fig. 5). The decerebrate preparation was more sensitive to the stimulant action of the drug. In the anesthetized group the stimulatory phase was followed by a progressive depression of respiration which reached the lowest value 4 hr after injection. Minute volume was depressed to —29.8 ± 5.2 % and end-expiratory % CO_2 was increased from 4.6 % to 8.05 ± 1.5 %. On the other hand, in the decerebrate-unanesthetized group the ventilation was normalized by the second hour and remained at the baseline level for 3 more hours.

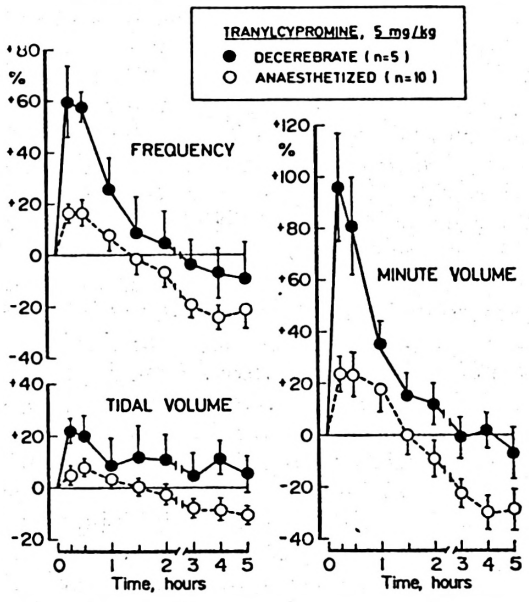

Fig. 5. *Time course of the respiratory effects induced by tranylcypromine (5 mg/kg, i.v.) in decerebrate-unanaesthetized* (A, *n=5) and intact brain-anaesthetized cats* (B, *n = 10).* Each symbol represents the mean ± S.E.M. of the percent change referred to the control value. Actual values at time 0: Frequency (breaths per min), *A:* 31.8 ± 2.8, *B:* 31.5 ± 2.1; tidal volume (ml), *A:* 34.6 ± 3.7, *B:* 29.3 ± 1.2; minute volume (ml), *A:* 1,500.0 ± 190.6, *B:* 947.1 ± 89.1.

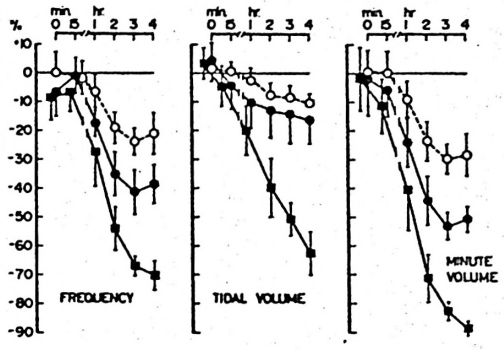

Fig. 6. *Time course of the respiratory effects induced by 5-HT in the presence of tranylcypromine (TCP).*
Values expressed at time 0 correspond to the effects observed 75 min after injection of TCP. Each symbol represents the mean ± S.E.M. of the percent change referred to the value obtained during the control period, before the administration of TCP. Actual values of the pre-TCP period: control TCP group (○) *see* legend of fig. 5; TCP+5-HTP 50 μg (●, n=7), frequency: 38.2 ± 1.8, tidal vol.: 22.5 ± 2.09, minute volume: 866.7 ± 103.05; TCP + 5-HT 500 μg (■, n = 5), frequency: 37.5 ± 2.0, tidal vol.: 24.0 ± 1.3, minute vol.: 805.8 ± 98.3.

50 and 500 μg of 5-HT were injected into the lateral ventricle of independent groups of anesthetized cats (n = 7 and 5, respectively) pretreated with tranylcypromine. Serotonin was administered 75 min after the injection of the inhibitor, when substantial brain MAO inhibition is known to occur (19). The values represented in fig 6 at time 0 correspond to the respiratory effects observed in each independent group, 75 min after the injection of tranylcypromine. Under these conditions, 5-HT enhanced the respiratory depression in a dose-dependent fashion: 50 μg of 5-HT intensified the depression of frequency and minute volume, and 500 μg markedly potentiated the depression of these two parameters plus tidal volume; CO_2 values could not be expressed because the level was elevated far

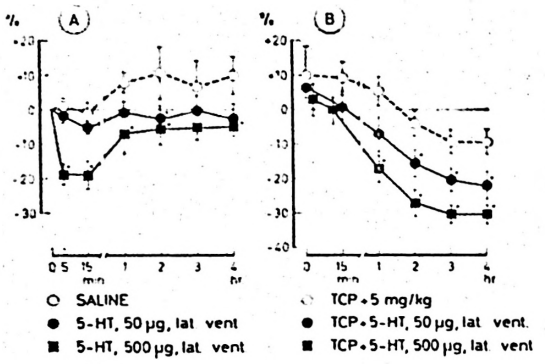

Fig. 7. *Time course of the blood pressure changes induced by 5-HT injected into the lateral ventricle of anaesthetized cats.* Each symbol represents the mean ± S.E.M. of the percent change referred to the value obtained during the control period. *A*. Actual values of mean blood pressure during the control period (mmHg), saline: 117.0±10.3, 5-HT 50 µg: 120.1 ± 5.2; 5-HT 500 µg: 122.0 ± 3.8. *B*. Values expressed at time 0 correspond to the effects observed 75 min after injection of TCP; actual values during the pre-TCP period: Control: 129.1 ± 6.4, TCP + 5-HT 50 µg: 130.8 ± 8.0, TCP + 5-HT 500 µg: 128.3 ± 7.8.

beyond the measuring capabilities of the capnograph. The respiratory depression of ventilation induced by 5-HT in MAO-inhibited animals began to be significant 1 hr after injection, and was progressively aggravated until the end of the experiment (fig. 2 and 6).

Effects of 5-HT on mean blood pressure. In the control group injected with artificial CSF, blood pressure rose slightly along the course of the 4 hr observation period (fig. 7 A). 5-HT 50 µg slightly reduced blood pressure during the first 40 min; thereafter the values were close to the baseline. Although they were always lower than in the control group, differences between both groups did not reach statistical significance. 500 µg induced a fall in blood pressure of —18.2 ± 5.7 during the first 15 min; one hour after injection the blood pressure was still significantly lower than that of the control group and then it was partially restored.

Tranylcypromine induced an immediate rise of blood pressure of +16.9 ± 5.9 %; at 75 min (0 time in fig. 7 B) the blood pressure was still above the baseline, and progressively declined to —9.3 ± 3.5 %. In the tranylcypromine pretreated cats, 5-HT induced a dose-related fall in blood pressure. Values at time 0 (75 min after tranylcypromine) were similar to those of the control group. After 50 and 500 µg intraventricular injections of 5-HT, blood pressure declined progressively to —22.1 ± 4.1 % and —30.1 ± 1.8 %, respectively, the values being significantly different from those of the control group.

Discussion

The present findings demonstrate that the introduction of 5-HT in the ventricular system of cats results in a depression of the activity of the respiratory and vasomotor centers. A reduction in the blood flow of the areas lying close to the ventricles, as a consequence of a direct vasoconstrictor effect, cannot be ruled out. However, since the systemic injection of 5-HT precursors brought about a similar depressant effects that was antagonized by the intracerebral injection of a l-aromatic aminoacid decarboxylase inhibitor (18), it seems reasonable to conclude that 5-HT exerts an inhibitory influence on these medullary centers. MAO inhibition potentiated the depressant effect of 50 and 500 µg of 5-HT by increasing the magnitude and duration of the depression on the frequency as well as on the amplitude generating mechanisms. In this regard, it is pertinent to observe that, in the control anesthetized group, tranylcypromine itself was able to depress respiration at a time when endogenous 5-HT is known to become elevated (20), and after the early amphetamine-like action was vanished. Indeed, the anesthe-

tic state seems to facilitate the moderatory influence of 5-HT on respiration; but in any case, the fourth ventricle studies were able to localize the action of 5-HT, since the direct contact of the amine with the pontomedullary region induced similar effects to those observed in the lateral ventricle group. It must be pointed out, however, that the respiratory centers were much more sensitive to the action of 5-HT than the vasomotor centers.

Our data do not contradict the previous findings of other workers (14, 19) who observed a tachypneic response during the first 30 min after injection in the lateral ventricle. The administration of 500 μg in the lateral ventricle induced a shortlasting increase in respiratory frequency concurrent with a reduction of tidal volume and alveolar ventilation, as inferred from the end-expiratory CO_2 values. This particular effect not only was transient but it was followed by a persistent and progressive reduction in ventilation, which was potentiated, right from the time of injection, by MAO inhibition. No stimulation of breathing, however, was present when the amine was injected into the fourth ventricle of anesthetized cats. Therefore we can conclude that the direct action of 5-HT on the respiratory center is characterized by depression, and that the transitory stimulant effect results from the action of 5-HT on suprapontine structures. Other drugs, like morphine, that depress the respiratory center have been also shown to stimulate briefly the respiratory frequency when are injected into the third ventricle (16). In addition to the depression of frequency, 5-HT reduced significantly the tidal volume and the ventilatory response to CO_2. These results indicate that 5-HT alters the CO_2 responsiveness of the respiratory center, thereby upsetting the mechanisms involved in respiratory control.

The depressant effect of intraventricular 5-HT on blood pressure confirms the results of other investigators (7). The results support the hypothesis that serotonergic activity in the caudal brain stem depresses the sympathetic outflow released from the vasomotor center (34); in fact, ADAIR *et al.* (1) have shown that the stimulation of specific serotonergic areas in the medulla, such as the nucleus raphe obscurus and nucleus raphe magnus, elicits depressor responses in the cat.

The effect of 5-TH on the activity of the respiratory and vasomotor centers can be considered as a particular feature of the more generalized action of serotonin in the central nervous system which in many respects is being considered as moderatory of brain behaviour (36). Serotonergic structures participate actively in antinociception (5, 8, 15, 35), and cortical synchronization has been reported to occur when 5-HT is introduced into the ventricular system (27), or is directly applied to the area postrema (33) and nucleus of the solitary tract (26). A dose-dependent decrease in locomotor activity has been also produced by intraventricular infusion of 5-HT in rats (37) and mice (22). Present evidence indicates that an increase in the activity of serotonergic structures occurs during some phases of sleep (24, 25); and since a reduction of the ventilatory response to CO_2 has been demonstrated during sleep (13), it is tempting to speculate that this reduction might be the consequence of a prevalent inhibitory action of the serotonergic input on the brain stem structures during sleep.

Although the doses used in this study are supraphysiological, it must be considered that serotonergic terminals exist in the walls of the cerebral ventricles and in the periventricular system (4, 10, 32); therefore, a substantial part of the serotonin that penetrated into the nervous tissue was probably taken up and selectively stored in the nerve endings of serotonergic neurones (2, 28), thereby preventing a portion of the amine to act directly upon the serotonergic receptors

located in the effector cells. When 5-HT has been applied by microiontophoresis to the brain stem neurones, an excitatory response has been frequently recorded (9, 11). Nervertheless the neurones were not functionally identified, and some depressant responses were also observed. Whether the specific neurones involved in the function of the respiratory and vasomotor centers are actually depressed by the directly applied 5-HT remains to be solved. Alternatively, the exogenous serotonin might activate presynaptic receptors thereby reducing the activity of 5-HT neurones (3, 21). It would imply that the normal function of the serotonergic neurones would be stimulatory rather than depressant. This possibility seems unlikely in view of the fact that inhibition of 5-HT synthesis by p-chlorophenylalanine results in the stimulation of the respiratory (17, 30) and vasomotor activities (23). Finally, it is also possible that the injected 5-HT was unspecifically taken up into noradrenergic terminals, leading to a displacement of noradrenaline and activation of adrenergic receptors. The respiratory depression would be the consequence of this activation: in fact, vasodepression is known to occur after noradrenergic activation (12). But as far as respiration is concerned, this hypothesis seems unlikely since studies performed in rats with amphetamine suggest that the respiratory stimulation elicited by this drug is the consequence of the activation of α-adrenergic mechanisms (31).

Acknowledgments

This work was partially supported by a grant of the Spanish National Health Service. The technical assistance of Ms. María J. Astrain is gratefully acknowledged.

Resumen

Se estudia en gatos ligeramente anestesiados la influencia de la 5-dihidroxitriptamina (5-HT) sobre la actividad de los centros respiratorio y vasomotor, mediante la inyección de 5-HT en un ventrículo lateral y en el IV ventrículo. A las dosis de 50 y 500 μg, la 5-HT inyectada en el ventrículo lateral produjo un breve aumento de frecuencia o de volumen corriente, seguido de una disminución prolongada de la frecuencia, volumen corriente y volumen minuto, que guardó relación con la dosis, junto con aumento del CO_2 tele-espiratorio. La 5-HT deprimió la respuesta del centro respiratorio al CO_2, así como los niveles de presión arterial. La inhibición de la monoamino oxidasa con tranilcipromina potenció los efectos depresores de la 5-HT. En el IV ventrículo la 5-HT, a la dosis de 50 μg, deprimió la respiración de modo similar al producido por la misma dosis en el ventrículo lateral, con la diferencia de que no estimuló inicialmente la actividad respiratoria.

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