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Role of 5-HT_{1A} and 5-HT_2 Receptors in the Aversion Induced by Electrical Stimulation of Inferior Colliculus

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MELO, L. L. AND M. L. BRANDÃO. *Role of 5-HT_{1A} and 5-HT_2 receptors in the aversion induced by electrical stimulation of inferior colliculus.* PHARMACOL BIOCHEM BEHAV 51(2/3) 317-321, 1995. — In addition to being a relay station for auditory pathways in the brainstem, the inferior colliculus may also be part of a brain system commanding defensive behavior. In the present work, we present evidence for the serotonergic modulation of the neural substrate of aversion in this structure. Rats implanted with an electrode-cannula in the inferior colliculus were placed inside a shuttle-box and submitted to a switch-off paradigm. Microinjections of zimelidine, a 5-HT uptake blocker, caused dose-dependent increases in latency and reductions in the frequency of switch-off responses to the inferior colliculus electrical stimulation. The 8-OH-DPAT, a classical 5-HT_{1A} agonist, and α-methyl-5-hydroxytryptamine, a highly selective 5-HT_2 agonist, injected directly into the inferior colliculus also produced clear antiaversive effects in a dose-dependent manner. The antiaversive effect produced by α-methyl-5-hydroxytryptamine was attenuated by the systemic administration of ketanserin, a preferential 5-HT_2 receptor antagonist. These results suggest that serotonergic mechanisms modulate the neural substrates commanding defensive behavior in the inferior colliculus, probably through a cooperative mechanism with the activation of 5-HT_{1A} and 5-HT_2 receptors.

Inferior colliculus 5-HT_{1A} receptors 5-HT_2 receptors Aversion Switch-off behavior

BEHAVIORAL reactions such as affective defense and escape have been reported following electrical stimulation of a set of structures in the brain composed of the medial hypothalamus, amygdala, dorsal periaqueductal gray (DPAG), and deep layers of superior colliculus. Together, these structures form a system that has been termed the brain aversion system (BAS) (11).

Much evidence has demonstrated that serotonin (5-HT) plays an inhibitory role in the neural substrates of aversion in the DPAG (1,11,13). Thus, in rats with electrode cannulae (chemitrodes) implanted into this structure, microinjection of either 5-HT or the 5-HT receptor agonist 5-methoxy-*N,N*-dimethyltryptamine raised the aversive threshold of brain electrical stimulation dose-dependently. This antiaversive effect was antagonized by previous microinjection into the DPAG of 5-HT_2 receptor blockers ritanserin and ketanserin, suggesting a possible anxiolytic effect of 5-HT mediated by 5-HT_2 receptors in the DPAG (11,24).

The inferior colliculus is a primary acoustic structure of the brainstem that has been implicated in the processing of aversive responses (4). It seems that the same modulatory mechanisms present at the DPAG level are also operative in the inferior colliculus as microinjections of bicuculline, a $GABA_A$ antagonist, into this structure produce behavioral activation together with autonomic responses resembling the defense reaction, suggesting a GABAergic inhibitory tonic control (5). It has been suggested that at least part of the anxiolytic action of the benzodiazepines is due to an enhancement of GABAergic activity in the inferior colliculus (21). Besides, opioid activation from the μ-receptor type also decreases the reactivity of the aversion substrates in the inferior colliculus (7), and microinjection of *N*-methyl-D-aspartate (NMDA) produced a behavioral activation with jumps similar to those seen after electrical stimulation of this structure (4,6).

To explore the role of 5-HT in the aversive behavior induced by inferior colliculus stimulation, we analyzed the effects of the 5-HT uptake blocker, zimelidine, 5-HT_{1A} (8-OH-DPAT) and 5-HT_2 (α-methyl-5-hydroxytryptamine) agonists

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microinjected directly in the inferior colliculus of rats submitted to a switch-off procedure. We also verified whether the preferential 5-HT_2 receptor blocker ketanserin (10,17), when injected IP, was able to antagonize the antiaversive effect of α-methyl-5-OH-tryptamine.

METHOD

Animals

Male Wistar rats from the animal house of the Campus of Ribeirão Preto of the University of São Paulo were used. These animals, weighing 250–300 g, were housed in individual Plexiglas-walled cages under a 12 L : 12 D cycle (lights on at 06:00 h) at 23 ± 1°C, and given free access to food and water throughout the experiment.

Surgery

The animals were anesthetized with sodium pentobarbital (45 mg/kg, IP) and fixed in a stereotaxic frame (David Kopf, Tujunga, CA). A chemitrode made of a stainless-steel guide-cannula (OD 0.6 mm, ID 0.4 mm, and length 13 mm) glued to a brain electrode (160 μm) was implanted in the midbrain, aimed at the inferior colliculus. The electrode was made of stainless-steel wire, 160 μm in diameter, insulated except at the cross section of the tip reaching 3 mm below the lower end of the cannula. The upper incisor bar was set at 3.3 mm below the interaural line such that the skull was horizontal between bregma and lambda. The chemitrode was introduced vertically using the following coordinates with the lambda serving as the reference for each plane: posteroanterior, 1.2 mm posterior to lambda; mediolateral, 1.5 mm; and dorsoventral, 4.5 mm. The chemitrode was fixed to the skull by means of acrylic resin and three stainless-steel screws. The electrode wire was connected to a male pin, parallel to the outer end of the cannula. Together they could be plugged into an amphenol socket at the end of a flexible electrical cable and used for brain stimulation. At the end of the surgery each guide-cannula was sealed with a stainless-steel wire to protect it from congestion.

Apparatus

One week after surgery, the rats were placed in a circular enclosed arena 60 cm in diameter and 50 cm high, placed in an isolated room illuminated with a 40-W fluorescent lamp (350 lx at the arena floor level). The rats were allowed a 15-min period of habituation in the enclosure. The brain was stimulated electrically by means of a sine-wave stimulator (20). The stimulation current was monitored by measuring the voltage drop across a 1-K resistor with an oscilloscope (Labo, São Paulo, Brasil). Brain stimuli (AC, 60 Hz, 15 s) were presented at 1-min intervals with the current intensity increasing by steps of 1.4 μA (rms) for measurements of the escape threshold. The escape threshold was operationally defined as the lowest current intensity that produced running (galloping) or jumping in two successive ascending series of electrical stimulation. At this point, animals with an escape threshold > 70 μA (rms) were removed from the experiment.

The shuttle-box consisted of two compartments 30 × 25 × 25 cm with a 2.5-cm barrier between them, and was equipped with four photoelectric cells equally spaced on the back wall. This arrangement allowed the recording of locomotor activity each time the animal crossed the midline of the shuttle-box passing from one compartment to the other. The front door was made of Plexiglas, allowing observation of the animal inside the box. The grid floor consisted of bars spaced 2 cm apart. The rat was placed in the shuttle-box and had its brain electrode connected to a flexible wire cable, which gave ample room for movement inside the box. The cable, in turn, was connected to the stimulator by means of a mercury swivel mounted on the top of the experimental chamber. The animals were allowed a 10-min habituation period. Next, brain stimulation was applied at a current intensity 5% below the escape threshold previously determined in the open field. The adequacy of this current intensity level for the switch-off procedure was chosen on the basis of preliminary experiments. A session consisted of a series of 10 electrical stimuli (AC, 60 Hz, 10 s) applied through the implanted electrode. Two successive stimuli were separated by a 1-min interval. Whenever a rat passed from one compartment to the other, brain electrical stimulation was immediately switched off. If no switch-off response occurred, the stimulus lasted 10 s. Latencies and number of switch-off responses were individually recorded by digital counters. Each rat was submitted to a maximum of three sessions while the escape threshold remained < 70 μA, rms. These experiments were carried out under low light conditions (20 lx at the shuttle-box floor level).

Microinjection Procedures

Immediately after the recording of baseline values in the control session in the shuttle-box, the animals were gently wrapped in a cloth and hand held, and a thin glass needle (70–90 μm OD) was introduced through the guide-cannula until its lower end was 3 mm below the guide-cannula, reaching the same depth as the electrode tip. The injection needle was linked to a 5-μl Hamilton syringe by means of polyethylene tubing. A volume of 0.2 μl was injected over 20 s. The displacement of an air bubble inside the polyethylene (PE-10) catheter connecting the syringe needle to the intracerebral needle was used to monitor the microinjection. Following the end of the injection, the microinjection needle was held inside the brain for 10 s. After 30 min, the animals were then returned to the arena or the shuttle-box for threshold redetermination or a posttreatment switch-off session. The animals were rested for at least 24 h between treatment tests. No more than three microinjections were given to the same rat. Independent groups of animals were used for evaluating drug effects on escape thresholds and switch-off responses.

Drugs

Zimelidine (RBI), α-methyl-5-OH-tryptamine (RBI), and 8-OH-DPAT (RBI) were each dissolved in physiologic saline (0.9%) shortly before use. Physiologic saline also served as vehicle control. IP injections of ketanserin (Janssen Pharmaceutica, Belgium) were made with doses of 1.0 and 10.0 mg/kg, in a volume of 1 ml/kg. For intracerebral injections, the doses used were 20 and 40 nmol for zimelidine, 2.0 and 5.0 nmol for α-methyl-5-OH-tryptamine, and 3.0 and 6.0 nmol for 8-OH-DPAT. Intracerebral injections were given in a volume of 0.2 μl.

No more than three microinjections were given to the same rat. To measure the effects of drug injections on the aversive effects of the electrical stimulation of the inferior colliculus, the animals were tested once before and then 15 min after intracerebral injections. IP injections of ketanserin were made 10 min before the microinjections of saline or α-methyl-5-OH-tryptamine. The time interval between drug injection and the behavioral tests were chosen on the basis of pilot experiments.

Analysis of Results

The results are reported as means ± SEM (N = 8 for each group). Results were analyzed by means of a one-way analysis of variance (ANOVA). Duncan posthoc comparisons were carried out if significant overall F-values were obtained. When a p value is cited with no further indication, it resulted from the Duncan test.

Histology

Upon completion of the experiments, the animals were deeply anesthetized with sodium pentobarbital and perfused intracardially with saline followed by formalin solution (10%). Next, the brains were removed and frozen. Three days later, serial 50-μm brain sections were cut using a microtome and stained with neutral red to localize the positions of the electrode tips according to the Paxinos and Watson atlas (22). Data from rats with electrode tips located in sites outside the inferior colliculus were not included in the statistical analysis.

RESULTS

The electrode tips were situated inside the central nucleus of the inferior colliculus, as illustrated in Fig. 1. Because the lower ends of both the injection needle and the electrode tip reached 3 mm below the guide cannula of the chemitrode, brain injections were made close to the electrode sites.

Figure 2 illustrates the effect of zimelidine microinjected in the inferior colliculus. Microinjection of zimelidine produced an increase of latencies [$F(2, 21) = 33.02$, $p < 0.01$] and a decrease of frequency [$F(2, 21) = 36.96$, $p < 0.01$] of flight responses. This effect was due to the dose of 40 nmol/0.2 μl ($p < 0.05$).

As shown in Fig. 3, microinjection of 8-OH-DPAT 10 min before the experimental session raised the latencies [$F(2, 21) = 26.26$, $p < 0.01$] and decreased the frequencies [$F(2, 21) = 21.50$, $p < 0.01$] of switch-off responses. Posthoc comparisons showed significant effects ($p < 0.05$) for both parameters only for the dose of 6.0 nmol/0.2 μl.

Figure 4 shows that intracerebral injection of α-methyl-5-OH-tryptamine in the inferior colliculus also promoted an increase of latencies [$F(2, 21) = 11.80$, $p < 0.01$] and a decrease of frequencies [$F(2, 21) = 14.51$, $p < 0.01$] of switch-off responses, in a dose-dependent way.

Figure 5 shows that IP injection of ketanserin reversed the antiaversive effect of 5 nmol of α-methyl-5-OH-tryptamine injected 10 min later in the inferior colliculus. A one-way ANOVA showed significant effects of drug interaction related

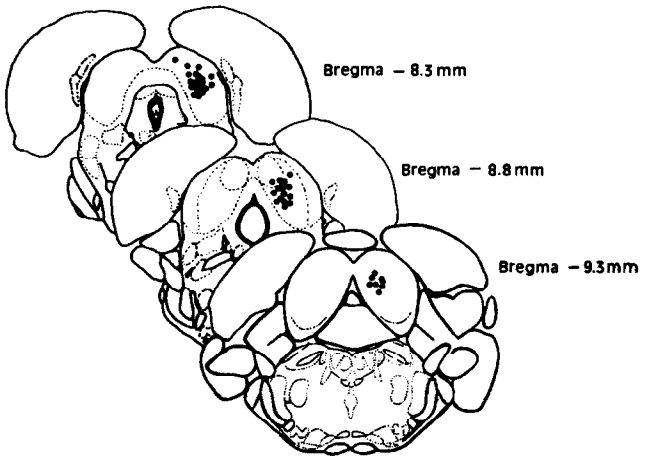

FIG. 1. Location of electrode sites on a cross section from Paxinos and Watson's rat brain atlas (22). Figures represent the atlas coordinates in micrometers, posterior to bregma.

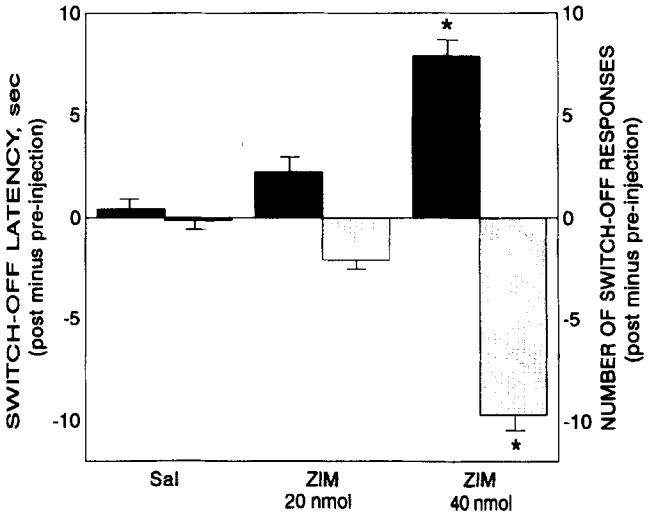

FIG. 2. Antiaversive effect of 5-HT reuptake blocker, zimelidine (ZIM, 20, and 40 nmol in 0.2 μl), microinjected into the inferior colliculus on the latencies (s) and frequencies (number of switch-off responses) of escape behavior induced by electrical stimulation of this structure. Filled columns (latencies) and hatched columns (frequencies) represent the average of the difference between escape responses in sessions post- and preinjection. Bars represent the SEM. Each session consisted of 10 escape trials. Injections were made 15 min before the experimental session. n = 8. *Different from control (SAL, saline microinjections, 0.2 μl) at $p < 0.05$, Duncan test after ANOVA.

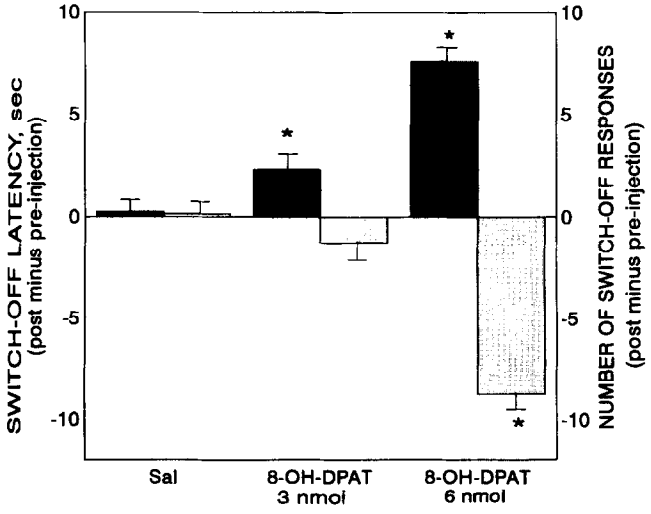

FIG. 3. Effects of local administration into the inferior colliculus (inferior colliculus) of 8-OH-DPAT (3 and 6 nmol in 0.2 μl) on the latencies and frequencies (number of switch-off responses) of escape behavior from inferior colliculus electrical stimulation. Other specifications as in Fig. 2.

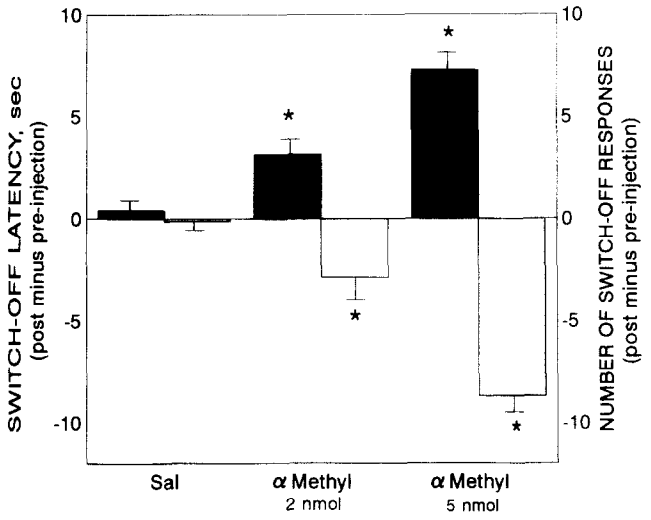

FIG. 4. Effect of α-methyl-5-OH-tryptamine (2.0 and 5.0 nmol in 0.2 μl) microinjected into the inferior colliculus on the latencies (s) and frequencies (number of switch-off responses) of escape behavior induced by electrical stimulation of this structure. Other specifications as in Fig. 2.

to inferior colliculus microinjections of α-methyl-5-OH-tryptamine and ketanserin for both parameters: frequency [$F(3, 28) = 4.67$, $p < 0.01$] and latency [$F(3, 28) = 4.37$, $p < 0.01$] of switch-off responses. Posthoc analysis revealed that 10 mg/kg of ketanserin injected before microinjections of saline into the inferior colliculus did not change latencies and frequencies of switch-off responses and that the reversal of the antiaversive effect of 5 nmol of α-methyl-5-OH-tryptamine was due to the dose of 10 mg/kg of ketanserin ($p < 0.05$).

DISCUSSION

A large body of evidence from behavioral studies has pointed to an involvement of the inferior colliculus in the integration of defensive behavior in the brain (4–7). Recently, Silveira at al. (25), using immunochemical detection of Fos, the protein product of the immediate early gene *c-fos*, showed that the central nucleus of this structure was strongly labeled after 15-min exposure to the elevated plus-maze. However, when aversive sites in the periaqueductal gray matter were electrically stimulated there was no increase in *c-fos*-like immunoreactivity in the central nucleus of the inferior colliculus (23). As we discuss later, the way the inferior colliculus participates in the brain aversion system still needs clarification.

We have shown that microinjection of $GABA_A$ receptors blockade in the rat inferior colliculus results in escape behavior along with neurovegetative changes such as increases in mean blood pressure and heart rate (5), and that microinjection of muscimol, a $GABA_A$ agonist, or midazolam, a benzodiazepine, and opioids into inferior colliculus clearly attenuated the aversive effects of the electrical stimulation of this structure (7,21). Also, when microinjected into the inferior colliculus N-methyl-D-aspartate (NMDA) produced a behavioral activation with jumps similar to those seen after electrical stimulation of this structure (6). All these data favor evidence already obtained for other BAS structures such as DPAG and MH, that GABA, opioids, and mechanisms mediated by amino acids may be important for the processing of aversive information into the inferior colliculus.

The present data indicate that endogenous serotonin probably exerts a modulatory role in the circuitry that commands aversive reactions at the level of the inferior colliculus. In fact, zimelidine microinjected directly into the inferior colliculus attenuated the aversive consequences of the electrical stimulation of this structure. These findings are in agreement with previously reported results showing that microinjection of this 5-HT reuptake blocker into the DPAG also produced antiaversive effects (1). This suggests that 5-HT may exert a similar role in both structures. This effect seems to be due to the activation of 5-HT_2 receptors, as microinjections of α-methyl-5-OH-tryptamine, a 5-HT_2 receptor agonist (12,17), produced similar antiaversive effects. That IP injection of ketanserin, a 5-HT_2 blocker, exhibited a potent effect in reversing the antiaversive action of α-methyl-5-OH-tryptamine microinjected into the inferior colliculus demonstrates additional evidence for the involvement of 5-HT_2 receptors in this effect. Ketanserin when administered alone at the dose we used neither caused any apparent alteration in the animal's behavior nor changed the reactivity of the inferior colliculus to the electrical stimulation of the inferior colliculus at the escape threshold. A lack of effect of 5-HT blockers injected in other BAS structures suggesting a phasic modulatory role played by 5-HT on the neural substrates of defensive behavior has been extensively reported (1,11,24).

Activation of 5-HT_{1A} receptors also results in antiaversive effects, as observed in several studies. An anxiolytic profile for 8-OH-DPAT, a 5-HT agonist with high affinity to 5-HT_{1A}

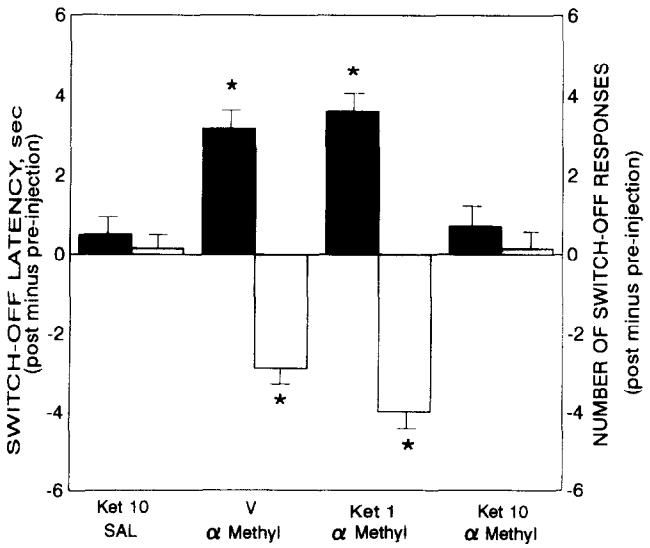

FIG. 5. Antagonism by ketanserin (Ket) of the antiaversive effect of microinjections of α-methyl-5-OH-tryptamine into the inferior colliculus (2.0 nmol/0.2 μl). The 5-HT antagonist ketanserin (1.0 and 10 mg/kg) or its vehicle (V) were administered, IP, 10 min before the 5-HT_2 agonist. The microinjections of α-methyl-5-OH-tryptamine and saline (SAL) were made inside the central nucleus of inferior colliculus (0.2 μl in 30 s). Columns represents the mean difference between the escape responses determined 15 min after the intracerebral injection and immediately before the IP injection. Vertical bars are the SEM for eight rats. *Different from control (ketanserine, IP + saline microinjections into the inferior colliculus, 0.2 μl) at $p < 0.05$, Duncan test after ANOVA. Other specifications as in Fig. 2.

receptors, when administered systemically, has been reported by many authors (9,19,26). Activation of these 5-HT receptors also mediates antiaversive effects when the defensive behavior is induced by DPAG stimulation (2).

Whereas electrophysiologic studies have indicated appreciable concentrations of 5-HT_{1A} and 5-HT_2 receptors in DPAG (3,18), evidence is still missing concerning the inferior colliculus. However, immunohistochemical reports have described appreciable amounts of serotonergic fibers in the inferior colliculus (27). These neurons seem to originate mainly from the dorsal raphe nucleus (14). These studies provide further support for 5-HT involvement in the modulation of the defense reaction suggested by the present study.

It is not surprising that a structure concerned with the perception of environmental auditory stimuli, such as the inferior colliculus, could be related to a defense reaction. In this regard other structures linked to the processing of visual stimulation, such as the superior colliculus, have also been suggested to participate in the brain aversion system (8). These authors have shown that the rodent SC is involved both in orienting toward and approaching novel stimuli, and in avoiding or escaping them. It is likely that in the inferior colliculus there also exists similar defense-related mechanisms that are activated by aversive auditory stimuli. However, it is important to note that not every aversive stimulation recruits aversive neural mechanisms in the inferior colliculus. In this respect, one possibility that has been raised is that the pathway underlying conditioned emotional responses involves transmission through the inferior colliculus to the medial geniculate body, and from there directly to the amygdala (15,16).

Our study shows that besides GABA-benzodiazepine, opioid, and EAA-mediated mechanisms, 5-HT also modulates phasically aversive states in the inferior colliculus, probably through a combined activation of 5-HT_{1A} and 5-HT_2 receptors.

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REFERENCES

1. Audi, E. A.; Aguiar, J. C.; Graeff, F. G. Mediation by serotonin of the antiaversive effect of zimelidine and propranolol injected into the dorsal medbrain central grey. J. Psychopharmacol. 2:26–32; 1988.
2. Beckett, S. R. G.; Lawrence, A. J.; Marsden, C. A.; Marshall, P. W. Attenuation of chemically induced defence response by 5-HT_1 receptor agonists administered into the periaqueductal gray. Psychopharmacology 108:110–114; 1992.
3. Brandão, M. L.; Lopez-Garcia, J. A.; Graeff, F. G.; Roberts, M. H. T. Electrophysiological evidence for excitatory 5-HT_2 and depressant 5-HT_{1A} receptors on neurones of the rat midbrain tectum. Brain Res. 556:259–266; 1991.
4. Brandão, M. L.; Melo, L. L.; Cardoso, S. H. Mechanisms of defense in the inferior colliculus. Behav. Brain Res. 58:49–55; 1993.
5. Brandão, M. L.; Tomaz, C.; Leão Borges, P. C.; Coimbra, N. C.; Bagri, A. Defence reaction induced by microinjection of bicuculline into the inferior colliculus. Physiol. Behav. 44:361–365; 1988.
6. Cardoso, S. H.; Coimbra, N. C.; Brandão, M. L. Escape behavior induced by microinjections of NMDA into the inferior colliculus. Behav. Brain Res. 63:17–24; 1993.
7. Cardoso, S. H.; Melo, L. L.; Coimbra, N. C.; Brandão, M. L. Opposite effects of low and high doses of morphine on neural substrates of aversion in the inferior colliculus. Behav. Pharmacol. 3:489–495; 1992.
8. Dean, P.; Redgrave, P.; Westby, G. W. M. Event or emergency? Two response system in the mammalian superior colliculus. Trends Neurosci. 12:137–147; 1989.
9. Engel, J. A.; Hjorth, S.; Svensson, K.; Carlsson, A.; Liljequest, S. Anticonflict effect of the putative serotonin receptor agonist 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT). Eur. J. Pharmacol. 105:365–368; 1984.
10. Fozard, J. R. 5-HT: The enigma variations. Trends Pharmacol. Sci. 8:501–506; 1987.
11. Graeff, F. G. Brain defense system and anxiety. In: Roth, M.; Burrows, G. D.; Noyes, R., eds. Handbook of anxiety, vol. 3. Amsterdam: Elsevier; 1990:307–354.
12. Hoyer, D. Molecular pharmacology and biology of 5-HT_{1C} receptors. Trends Pharmacol. Sci. 9:89–94; 1988.
13. Kiser, R. S. Jr.; Lebovitz, R. M. Monoaminergic mechanisms in aversive brain stimulation. Physiol. Behav. 15:47–56; 1975.
14. Klepper, A.; Herbert, H. Distribution and origin of noradrenergic and serotonergic fibers in the cochlear and inferior colliculus of the rat. Brain Res. 557:190–201; 1991.
15. LeDoux, J. E.; Iwata, J.; Pearl, D.; Reis, D. J. Disruption of auditory but not visual learning by destruction of intrinsic neurons in the medial geniculate body of the rat. Brain Res. 371:395–399; 1986.
16. LeDoux, J. E.; Sakagushi, A.; Reis, D. J. Subcortical efferent projections of the medial geniculate nucleus mediate emotional responses conditioned to acoustic stimuli. J. Neurosci. 4:683–698; 1986.
17. Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. ^{3}H Ketanserin (R 41468), a selective ^{3}H-ligand for serotonin 2 receptor binding sites. Mol. Pharmacol. 21:301–314; 1982.
18. Lovick, T. A. Serotonergic influence from nucleus raphe obscurus on neurones in the periaqueductal grey matter in the rat. Brain Res. 606:92–98; 1993.
19. Mansbach, R. S.; Geyer, M. A. Blockade of potentiated startle responding in rats by 5-hydroxytryptamine 1A receptor ligands. Eur. J. Pharmacol. 156:375–383; 1988.
20. Marseillan, R. F. A solid state sine wave stimulator. Physiol. Behav. 19:339–340; 1977.
21. Melo, L. L.; Cardoso, S. H.; Brandão, M. L. Antiaversive action of benzodiazepines on escape behavior induced by electrical stimulation of the inferior colliculus. Physiol. Behav. 51:557–562; 1992.
22. Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. New York: Academic Press; 1986.
23. Sandner, G.; Oberling, P.; Silveira, M. C.; DiScala, G.; Rocha, B.; Bagri, A.; Depoortere, R. What brain structures are active during emotions? Effects of brain stimulation elicited aversion on c-fos immunoreactivity and behavior. Behav. Brain Res. 58:9–18; 1993.
24. Schutz, M. T. B.; Aguiar, J. C.; Graeff, F. G. Antiaversive role of serotonin in the dorsal pariaquedutal grey matter. Psychopharmacology 85:340–345; 1985.
25. Silveira, M. C. L.; Sandner, G.; Graeff, F. G. Induction of Fos immunoreactivity in the brain by exposure to the eleveted plus-maze. Behav. Brain Res. 56:115–118; 1993.
26. Soderpalm, S.; Hjorth, S.; Engel, J. A. Effects of 5-HT_{1A} receptor agonists and L-5-HTP in Montgomery's conflict test. Pharmacol. Biochem. Behav. 32:259–265; 1989.
27. Steinbusch, H. V. M. Distribution of serotonin-immunoreactivity in central nervous system of the rat—Cell bodies and nerve terminals. Neuroscience 6:557–618; 1981.