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High Intensity Social Conflict in the Swiss Albino Mouse Induces Analgesia Modulated by 5-HT_{1A} Receptors

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CANTO DE SOUZA, A., R. L. NUNES DE SOUZA, I. R. PELÁ AND F. G. GRAEFF. *High intensity social conflict in the Swiss albino mouse induces analgesia modulated by 5-HT_{1A} receptors.* PHARMACOL BIOCHEM BEHAV **56**(3) 481–486, 1997.—Social conflict between mice produces analgesia in the attacked mouse. Both the magnitude and type (opioid or nonopioid) of this analgesia have been related to attack intensity and strain of mouse. In the present study low intensity social conflict (7 bites) did not produce analgesia, whereas high intensity - 30 and 60 bites - interactions produced, respectively, short-lasting (5 min) and very short-lasting (1 min) analgesia in Swiss albino mice, when compared with nonaggressive interaction (0 bite). The 30 bites aggressive interaction induced analgesia (AIIA) was not affected by IP injection of either naloxone (5.0 and 7.5 mg/kg) or diazepam (0.5, 1.0, 2.0 and 4.0 mg/kg). However, this attack-induced analgesia was reduced after IP administration of the 5-HT_{1A} agonists, gepirone (0.3 and 3.0 mg/kg) and BAY R 1531 (0.01 mg/kg). These results indicate that the analgesia induced by 30 bites social conflict in Swiss albino mice does not involve opioid and GABA-benzodiazepine (GABA-BZD) mechanisms. In addition, they suggest that high-intensity social conflict activates serotonergic pain modulatory systems that act through 5-HT_{1A} receptors.

Social conflict Analgesia Naloxone Diazepam 5-HT_{1A} agonists Swiss albino mice

SEVERAL studies have demonstrated antinociceptive reactions in animals exposed to stressful stimuli (1,2,4,6,23,31). Among these experimental settings is the confrontation between an aggressive resident animal and a nonaggressive intruder. The nonaggressive intruder is invariably attacked by the resident that has been rendered aggressive by a brief period of social isolation. The agonistic interaction induces scape-related behaviors, submissive/defensive postures and immobility in the attacked mouse that are accompanied by antinociception (for a review see (2,6,31).

At least two qualitatively different profiles of endogenous antinociception have been proposed, depending on whether the intruder is exposed to a mild (5–10 attack bites) or a prolonged (30–100 attack bites) social stress (for a review see (23). Involvement of opioid mechanisms has mainly been shown after enduring attack, in that this long-lasting (up to 60 min) form of analgesia (high intensity analgesia) was either reduced or prevented by opiate antagonists (13,15,16,28,29,34). In regard to antinociception elicited after a mild attack stress (low intensity analgesia), the role of nonopioid mechanisms has been emphasized. This view is mainly based on experiments in which naloxone (7,17,30) and naltrexone (28) failed to antagonize this short-lasting (less than 10 min) analgesia. On the other hand, selective neuronal and nonneuronal benzodiazepine antagonists Ro 15-1788 and Ro 15-3505, and the agonist diazepam prevented low intensity analgesia (18,19, 21,22), whereas these compounds did not affect the high intensity analgesia observed after prolonged attack (18). In addition, the 5-HT_{1A} receptor agonists, 8-OH-DPAT (24), buspirone, gepirone, ipsapirone (25) and MDL 72832 (26), blocked

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the analgesic consequences of a mild social conflict. Therefore both serotonergic and GABA-benzodiazepine (GABA-BZD) mechanisms seem to be involved in low intensity analgesia.

Moreover, the degree of analgesia induced by social conflict depends on several factors, in addition to attack intensity. Among these are age and housing conditions of the opponent, the territory of confrontation and mouse genotype (8,33). Interestingly, the magnitude of social conflict analgesia correlates well with the sensitivity of different inbred mouse strains to the analgesic effect of morphine. DBA/2 and B6AF1 mice show potent analgesic reactions to both attack and morphine, whilst C57BL/6 mice as well as the f-receptor deficient CXBK strain, show only weak social conflict and morphine induced analgesia (8,12,13,32).

The purpose of the present study was to investigate the nociceptive response to social conflict in Swiss albino mice. Our interest to study this mouse strain has two reasons: (a) although the Swiss albino is one of the most widely used mouse strain there is a small number of studies in the literature investigating its pain sensitivity to social stress; and (b) as the Swiss albino is not an inbred strain, the study of its nociceptive reaction and underlying mechanisms may have ethological significance.

Therefore, the present study attempted to investigate (a) the characteristics of the nociceptive response of Swiss albino mice following different intensities of aggressive interactions (Experiment I); (b) opioid mechanism involvement on aggressive interaction induced analgesia (AIIA), through injection of the opiate antagonist naloxone (Experiment II); (c) nociceptive sensitivity upon morphine and naloxone injections (Experiment III) and (d) involvement of GABA-BZD and 5-HT_{1A} receptors on AIIA (Experiment IV).

METHOD

Experiment I. Effect of Aggressive Interaction Intensity on Nociception

Animals. Male Swiss mice weighing 23–25 g, had free access to food and water and were housed in groups of ten on a 12 h light cycle. The experiments were conducted during the light phase of the cycle, between 9:00 am and 4:00 p.m.

Procedures. Mice were handled once 24 and 48 h before the experiments. Each animal was introduced into an acrylic tube for 1-2 min and after this, the mouse was placed inside an individual cage for 5 min.

Nociception test. Analgesia was assessed by the tail-flick test. Each animal was placed into an acrylic tube and its tail laid across a nichrome wire coil that was heated by an electric current. The current raised the temperature of the coil at the rate of 9°C/s. The temperature was adjusted to give control tail-flick latencies (TFL) of 2.5–3.5 s. A cut-off of 6 s was employed to prevent tissue damage. All test mice (intruders) had three TFLs measured at 5-min intervals to ensure stability. Immediately after aggressive interactions (see below) TFL measurements were carried out at 1, 5, 10 and 20 min. Each TFL was normalized by calculating an index of analgesia (IA):

$$\text{IA} = \frac{(\text{test TFL}) - (\text{average baseline TFL})}{6 - (\text{average baseline TFL})}$$

Aggressive interaction. Immediately after baseline nociception measurement, each animal was introduced into the home cage of an aggressive opponent of the same strain. The test mouse was readily attacked by the resident and exposed to 7, 30 or 60 bites. These attacks lasted 1–4 min and, then, the aggressive mouse was taken out of the cage, so that the intruder mouse stayed inside the aggressor's home cage until the end of the nociception test. The aggressive dominant mice were selected from a group of animals housed singly for at least 4 wk, as described by Hüston and Bures (9).

Nonaggressive interaction. The procedure used to nonaggressive interactions was similar to to that described above under aggressive interaction, except that the test mouse was introduced to an nonaggressive opponent by a period of 2 min.

Experiment II: Naloxone on 30-Bites AIIA

Animals and procedure. Mice were handled once 24 and 48 h before the experiments. Each animal was introduced into an acrylic tube for 1-2 min, followed by an IP sham injection. After this, the mouse was placed inside an individual cage for 5 min.

Aggressive interaction. As in Experiment I, except that immediately after baseline nociception measurement, each mouse received IP drug or control injection and, 20 min later, was introduced into the home cage of an aggressive opponent of the same strain. The interaction was interrupted by the experimenter when the test mouse was exposed to 30 bites.

Drugs. Naloxone hydrochloride (Endo Laboratories) dissolved in physiological saline (0.9% NaCl).

Experiment III: Morphine and Naloxone on Nociception

Procedure. After baseline measurement of IA (see Experiment I) each animal received I.P injection of one the following solutions: 0.9% NaCl + 2.0 mg/kg morphine; 5.0 mg/kg naloxone + 2.0 mg/kg morphine or 7.5 mg/kg naloxone + 2.0 mg/kg morphine. Twenty minutes after pharmacological treatment the IA was assessed at 20, 25, 30 and 40 min after injection by the tail-flick test, as described above. There was no aggressive interaction in this experiment.

Experiment IV: Diazepam, Gepirone and BAY R 1531 on 30 Bites AIIA

The procedure of this experiment was similar to the Experiment II, except for the drugs used.

Drugs. Diazepam (Roche), gepirone hydrochloride (Bristol-Myers Co.) and BAY R 1531 (Bayer), were used. All compounds were dissolved in physiological saline (0.9% NaCl), except for diazepam that was suspended in saline with 2% Tween 80.

Statistical analysis. Data were analysed by a two-way between-within ANOVA followed by the Duncan test (between group comparisons) or Dunnet test (within group comparisons).

RESULTS

Experiment I: Effect of Interaction Intensity on Nociception

Figure 1 shows the IA of Swiss albino mice recorded 5 min before (baseline) and 1, 5 10 and 20 min after nonaggressive (0 bite) or aggressive interactions of 7, 30 or 60 bites, respectively. ANOVA showed significant effects of time, $F(4, 156) = 13.72$, $p < 0.0001$, and attack intensity, $F(3, 39) = 4.40$, $p = 0.009$, on AIIA. There was no significant attack intensity vs time interaction, $F(12, 156) = 1.22$, $p = 0.273$. Between group comparisons indicated that the 7-bites aggressive interaction did not significantly increase the IA when compared with nonaggressive interaction. The 30-bites aggressive interaction, however, significantly increased the IA at the 1st and 5th min

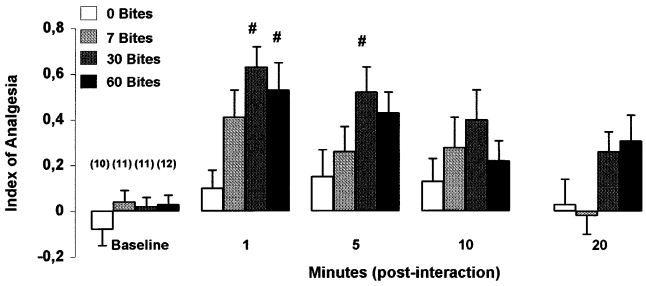

FIG. 1. Index of analgesia (IA) recorded pre- (baseline) and post- (1, 5, 10 and 20 min) nonaggressive (0 bite) and aggressive (7, 30 or 60 bites) interactions in Swiss albino mice. Data are presented as mean (± SE) of IA. Figures in parentheses indicate number of animals per group. # $p < 0.05$ compared with 0 bite group.

after confrontation as compared to the 0 bite control. The 60-bites attack significantly increased the IA at 1st min only. Within group comparisons along time indicated that the three aggressive interactions significantly increased ($p < 0.05$) the IA for different periods (7 bites: 1st min; 30 bites: 1st to 10th min; 60 bites: 1st to 5th min).

Experiment II: Lack of Effect of Naloxone on 30-Bites AIIA

Figure 2 shows the effect of naloxone on AIIA. The IA was recorded pre (5 min before) and post (1, 5, 10 and 20 min after) the 30-bites aggressive interaction. ANOVA revealed neither a significant effect of naloxone on AIIA, $F(2, 27) = 0.71$, nor a significant treatment vs time interaction, $F(8, 108) = 1.28$. However, there was a significant effect of time, $F(4, 108) = 13.12, p < 0.001$. Within-group comparisons along time indicated that aggressive interactions significantly increased ($p < 0.05$) the IA in every group (Saline: 1st and 5th min; Naloxone 5.0 mg/kg: 1st to 10th min; Naloxone 7.5 mg/kg: 1st to 20th min) when compared with baseline.

Experiment III: Effect of Morphine on Nociception and its Antagonism by Naloxone

Figure 3 shows the IA recorded 5 min before (baseline) and 20, 25, 30 and 40 min after IP injection of saline + 2.0

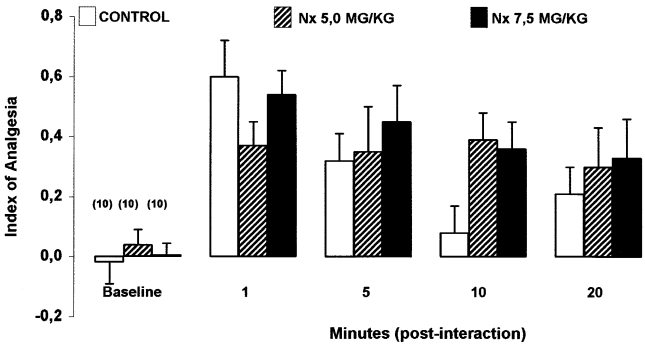

FIG. 2. Index of analgesia (IA) recorded pre- (baseline) and post- (1, 5, 10 and 20 min) 30 bites aggressive interaction in mice treated intraperitoneally with vehicle (control) or naloxone (5.0 and 7.5 mg/kg). Data are presented as mean (±SE) of IA. Figures in parentheses indicate number of animals per group. # $p < 0.05$ compared with control group.

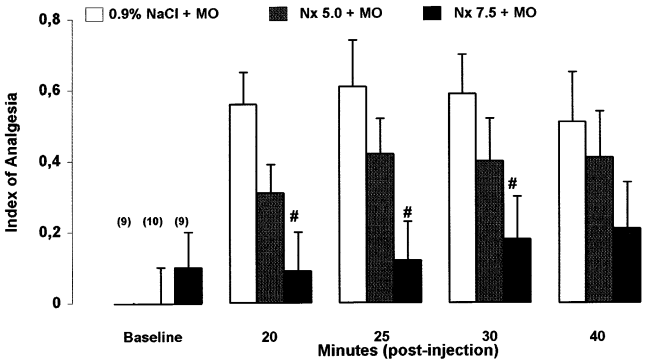

FIG. 3. Index of analgesia (IA) recorded pre- (baseline) and post- (20, 25, 30 and 40 min) 0.9% NaCl (IP) + morphine (2.0 mg/kg; S.C.) or naloxone (5.0 or 7.5 mg/kg; IP) + morphine (2.0 mg/kg; S.C.) treatement. Data are presented as mean (± SE) of IA. Figures in parentheses indicate number of animals per group. # $p < 0.05$ compared with control group.

mg/kg morphine ($n = 9$), 5.0 mg/kg naloxone + 2.0 mg/kg morphine ($n = 10$) or 7.5 mg/kg naloxone + 2.0 mg/kg morphine ($n = 9$). ANOVA revealed significant effects of time, $F(4, 100) = 8.87$, $p < 0.001$, and treatment $F(2, 25) = 4.82$, $p < 0.01$, but no significant treatment vs time interaction, $F(8, 100) = 1.84$, $p = 0.078$. Within-group comparisons along time indicated that morphine significantly increased ($p < 0.05$) the IA from the 20th to the 40th min. In addition, between-group comparisons revealed that 7.5 mg/kg naloxone reduced significantly the IA from 20th to 30th min, whereas 5.0 mg/kg naloxone did not significantly change morphine-induced analgesia.

Experiment IV: Effects of Diazepam, Gepirone and BAY R 1531 on 30-Bites AIIA

Diazepam. Figure 4A illustrates the effect of pretreatment with diazepam on AIIA. ANOVA showed that none of the four doses of the benzodiazepine used significantly affected AIIA, $F(4, 48) = 0.68$. The same analysis also revealed no significant treatment vs time interaction, $F(16, 192) = 1.72$, but a significant effect of time, $F(4, 192) = 29.14$, $p < 0.001$. Within-group comparisons along time (pre- vs post-interaction) indicated significant increases ($p < 0.05$) in IA when compared with baseline at the 1st and the 5th min (vehicle); the 10th min only (diazepam 0.5 mg/kg); from the 1st to the 10th min (diazepam 1.0 mg/kg) and from the 1st to the 20th min (diazepam 2.0 and 4.0 mg/kg).

Gepirone. As shown in Fig. 4B, gepirone attenuated AIIA. ANOVA indicated a significant overall drug effect on the IA, $F(2, 33) = 5.11, p < 0.012$. In addition, there was a significant effect of time, $F(4, 132) = 22.93$, $p < 0.001$ and a significant treatment vs time interaction, $F(8, 132) = 2.72$, $p < 0.008$. Between-group comparisons at each time revealed that both doses of the 5-HT$_{1A}$ agonist reduced significantly the IA in the 1st min. The highest dose also significantly reduced the analgesic response at the 20th min. Within-group comparisons along time indicated that aggressive interaction significantly increased ($p < 0.05$) the IA when compared with baseline in all groups (saline: 1st and 5th min; gepirone 0.3 and 3.0 mg/kg: 1st to 10th min).

BAY R 1531. In the same way as gepirone, BAY R 1531 decreased AIIA (Fig. 4C). ANOVA revealed an overall drug

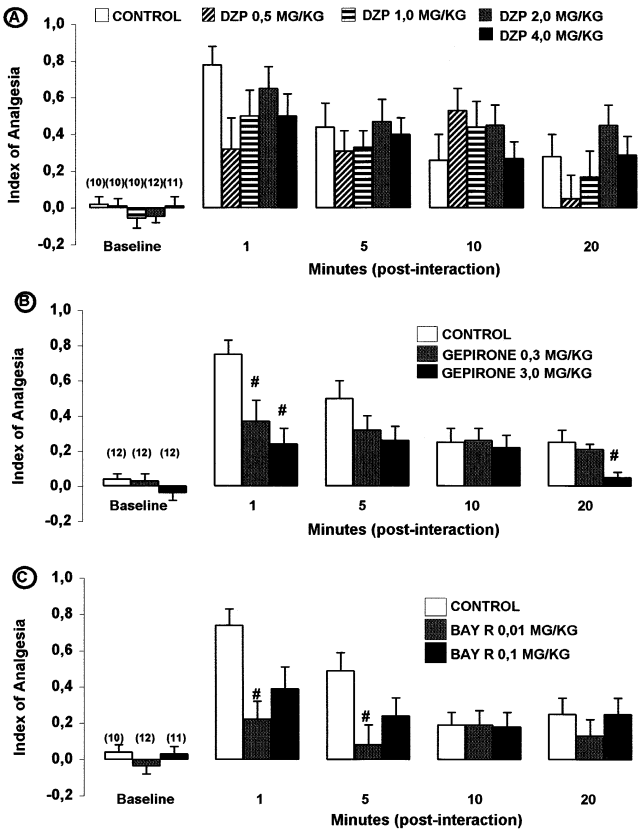

FIG. 4. Index of analgesia (IA) recorded pre- (baseline) and post- (1, 5, 10 and 20 min) 30 bites aggressive interaction in mice treated intraperitoneally with vehicle (control) and (A) diazepam (0.5, 1.0, 2.0 and 4.0 mg/kg); (B) gepirone (0.3 and 3.0 mg/kg, i.p.) or (C) BAY R 1531 (0.01 and 0.1 mg/kg). Data are presented as mean (± SE) of IA. Figures in parentheses indicate number of animals per group. #$p < 0.05$ compared with control group.

effect, $F(2, 30) = 4.05$, $p < 0.028$. The analysis also revealed a significant effect of time, $F(4, 120) = 13.85$, $p < 0.001$, and a significant treatment vs time interaction, $F(8, 120 = 2.51$, $p < 0.015$. Within-group comparisons along time showed significant analgesia at the 1st and 5th min after saline and at the 5th min only after 0,1 mg/kg of the drug. Between-group comparisons showed that the analgesic response induced by social conflict was significantly reduced by the lowest dose of BAY R 1531, both at the 1st and 5th minute. The highest dose of the drug was ineffective.

DISCUSSION

The present results indicate that Swiss albino mice experience analgesia following high-intensity aggressive interaction with a dominant mouse of the same strain. However, the magnitude and duration of the analgesic response was not directly proportional to attack intensity, since the 30-bites attack was more effective than both the 7-bites encounter, which caused no analgesia, and the 60-bites attack, which produced analgesia only in the 1st min. Nevertheless, the analgesia induced by the 30-bites attack was still short-lived, since it lasted no more than 5 min. A longer duration has been reported with certain inbred mouse strains. For instance, the DBA/2J and B6AF1 strains have analgesia up to 60 min following high intensity attack (30–100 bites). These strains also show short-lasting analgesia following a low intensity attack (5–10 bites). There are other strains, however, such as CXBK and C57BL/6J, in which high intensity attack produces only short-lasting analgesia, like the Swiss albino mice in the present results (for a review of strain effect on AIIA, see (8).

The present results have additionally shown that the 30-bites aggressive interaction seems to induce a nonopoioid type of analgesia in Swiss albino mice, since pretreatment with naloxone failed to block AIIA. This result contrasts with previous studies with other strains of mice using comparable stress intensity and the same dose range of naloxone, (7,13,16,34). On the other hand, it has also been reported that 1.0, 5.0 or 10 mg/kg naloxone (7,17) or 0.5 and 2.0 mg/kg naltrexone (28) did not block low intensity (5-10 bites) AIIA. Therefore, the 30-bites social conflict seems to produce a short-lasting nonopioid analgesia in Swiss albino strain of mice that is similar to the analgesia induced by low-intensity conflict in more sensitive strains.

The ineffectiveness of naloxone on AIIA shown by the present results could be an indication that the Swiss albino strain is devoid of pain-inhibitory opioid mechanisms. However, the present results showing that morphine induced long-lasting analgesia antagonised by naloxone does not support this hypothesis. This lack of correlation contrasts with reported results in the CXBK and B6F1 strains which show both a low sensitivity to AIIA and to morphine injection (13). Therefore, the Swiss albino strain may be of particular interest for the study of nonopioid analgesia. However, further studies using more selective opioid subtype receptor antagonists are also needed to establish the opioid involvement on this form of analgesia.

Several studies have implicated γ-aminobutyric acid-benzodiazepine (GABA-BZD) mechanisms in the mediation of nonopioid AIIA (18–23). In the present results, however, diazepam failed to block the analgesia induced by the 30-bites interaction in Swiss albino mice. This is probably another strain difference, since the mentioned studies have been performed in DBA/2 mice. As pointed out above, however, the intensity of social conflict was also different, i.e., 5–10 instead of 30 bites. Moreover, it is possible that higher doses of diazepam or more potent benzodiazepine agonists will be effective. Nevertheless, like in the present work, negative results with BZD agonists in DBA/2 mice undergoing low intensity social conflict have also been reported (19). Therefore, the role of GABA-BZD mechanisms in AIIA is still uncertain.

A wealth of experimental data implicates serotonergic mechanisms in nociception, although 5-HT has been suggested to either facilitate (3,14,37) or inhibit (10,11,27,35,36) nociceptive responses. The present results add to this evidence, since they show that intraperitoneal injection of the 5-HT_{1A} receptor agonists gepirone and BAY R 1531 reduced the magnitude of the analgesia caused by 30-bites social conflict in Swiss albino mice.

The 5-HT_{1A} receptor occurs both pre and postsynaptically in the central nervous system (CNS). The presynaptic receptors are localized on dendrites and soma of 5-HT raphe neurons, and their stimulation decreases neuronal firing rate. In turn, postsynaptic 5-HT_{1A} receptors are localized on neurons that do not contain 5-HT and receive 5-HT input. They are distributed in many areas of the CNS, the highest concentration being found in the hippocampus (38). In the present results, a broader range of doses of gepirone than of BAY R 1531 antagonized AIIA. This may indicate that stimulation of presynaptic 5-HT_{1A} receptors inhibits this type of analgesia,

since both drugs behave as full agonists on autosomic 5-HT_{1A} receptors, whereas on postsynaptic receptors only BAY R 1531 is a full agonist while gepirone acts as a partial agonist (5). It is even possible that stimulation of postsynaptic 5-HT_{1A} receptors facilitates AIIA, since in the present results the lowest dose of BAY R 1531 completely blocked the analgesia, but the highest dose was ineffective. These results may be explained by assuming that the lowest dose of BAY R 1531 (like gepirone) stimulated mainly presynaptic receptors. Additional stimulation of postsynaptic receptors by the highest dose of BAY R 1531 would override the effect of presynaptic receptor stimulation.

With systemic administration, however, it is impossible to localize the site of action of the above drugs. For this purpose, studies with intracerebral microinjection are currently under way in our laboratories.

It could be possible that some animals have experienced the 30-bites social conflict at shortest latencies than others. Also, the agonistic encounter could have been intensified or attenuated by the pharmacological treatment. Such possibilities could effect the analgesic response to the stress. However, it should be emphasized that the present study was designed to delimit this social stress to at most 4 minutes and, except with the highest doses of diazepam, none apparent behavioral disruption was detected following drug administration. Nevertheless, further studies are necessary to investigate if the above compounds influence the defeat latency and as consequence the analgesic response of the intruder mice.

In summary, the present results show that Swiss albino mice have a short-lived analgesic response to high-intensity (30-bites) intraspecific conflict that is not mediated by either opioid or GABA-benzodiazepine mechanisms. They also indicate that 5-HT may be involved in this modality of AIIA, through stimulation of 5-HT_{1A} receptors.

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