EFFECTS OF IPSAPIRON AND BAY R 1531 ON
LEARNED HELPLESSNESS

E.O. GRAEFF*, M.H.L. HUNZIKER*,**
and F.G. GRAEFF***

*Departamento de Psicologia Experimental, Instituto de Psicologia,
Universidade de São Paulo, 05508 São Paulo, SP, Brasil
**Departamento de Farmacologia, Faculdade de Ciências Médicas,
Universidade Estadual de Campinas, 13081 Campinas, SP, Brasil
***Laboratório de Psicobiologia, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto,
Universidade de São Paulo, 14049 Ribeirão Preto, SP, Brasil

The effects of the 5-hydroxytryptamine-1A (5-HT1A) receptor agonists on the learned helplessness test were investigated. Rats were submitted to a single session of 60 uncontrollable shocks (10-s duration, 1.0 mA, every 60 ± 40 s) and then treated twice daily with ip injections of either ipsapirone (13 mg/kg daily) or BAY R 1531 (0.375 mg/kg daily) for four consecutive days. On the last day, the animals were submitted to an escape test. The results showed that both drug treatments blocked the deficit in the escape learning (helplessness effect). These data suggest that drugs which stimulate 5-HT1A receptors have an antidepressant-like activity in this animal model of depression.

Key words: learned helplessness, uncontrollable shocks, ipsapirone, BAY R 1531, 5-hydroxytryptamine-1A receptor agonist, animal model of depression.

It is known that the serotonergic neurotransmission, among others, is affected by antidepressant drugs (1,2). Recently, it was shown that a partial 5-HT1A receptor agonist, ipsapirone (IPS), was able to improve symptoms of depression as well as of anxiety in neurotic patients (B. Kuemmel, Troponwerke, Köln, Federal Republic of Germany, personal communication). In addition, the full 5-HT1A agonist, BAY R 1531 (BAY), showed antidepressant-like activity in the antagonism of tetrabenazine, potentiation of amphetamine and forced swimming tests (3). These data prompted us to investigate the effects of BAY and IPS on the learned helplessness model of depression, since it has been shown that pharmacological and non-pharmacological treatments of human depression are active on this model, whereas drugs which are not antidepressant are ineffective (4).

Forty-eight male Wistar rats (3 months old at the beginning of the experiment), obtained from the rat colony of the State University of Campinas, were used. The animals were kept in individual cages with free access to food and water. The experiments were

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Correspondence: Dr. M.H.L. Hunziker, Departamento de Psicologia Experimental, Instituto de Psicologia, Universidade de São Paulo, Av. Prof. Mello Moraes, 1721, Cidade Universitária, 05508 São Paulo, SP, Brasil.
carried out during the light phase of a 12-h light/12-h dark cycle. The subjects were divided into groups of eight animals each. Half of the animals followed the procedure described below: on day 1 of the experiment, the rat was placed in a Plexiglass box (inner dimensions 21.5 x 21.5 x 21.0 cm) enclosed in a sound-attenuating cage and equipped with a grid floor of stainless steel bars. Sixty electric foot-shocks of 1 mA and 10 s of duration were delivered according to a variable time schedule with a mean interval of 60 s and a range from 20 to 100 s, during a single experimental session. Six hours after the end of the session, the first drug injection was applied, ip. On day 2, 3 and 4 of the experiment the animals were injected twice daily: in the morning, 18 h after the previous injection, and in the afternoon, 6 h after the last injection.

On day 5, the subject received only the morning injection and 30 min later was placed in the test chamber. The latter consisted of a two-way automated shuttlebox (inner dimensions 50.0 x 15.5 x 20.0 cm) made of Plexiglass, enclosed in a sound-attenuating chest and equipped with a grid floor of stainless steel bars. The box was divided into two equal compartments by a wall provided with a window (7.5 x 6.0 cm), 8.0 cm above the floor. Thirty electric foot-shocks of 1 mA were delivered according to a variable time schedule with a mean interval of 60 s and a range from 20 to 100 s, each shock representing an escape trial. The shocks were discontinued immediately after the rat had jumped through the window to the opposite compartment. If the animal failed to jump within 10 s, the shock was automatically turned off. The time between the onset and the offset of shock was considered to be the response latency/trial duration. The other half of the animals underwent the same procedure as described above, except that they were not submitted to the uncontrollable shock session on day 1 of the experiment. The animals were injected ip with IPS (3.0 mg/kg in the morning and 10.0 mg/kg in the afternoon), BAY (0.125 mg/kg in the morning and 0.25 mg/kg in the afternoon) or distilled water (controls). IPS was dissolved in distilled water and BAY was dissolved in saline. The morning injections were 1 ml/kg and the afternoon injections 2 ml/kg.

Rats previously exposed to uncontrollable shocks and treated with daily injections of water showed a marked escape learning deficit when compared to non-shocked rats (Figure 1, panel A). Analysis of variance indicated that the difference between these two groups of rats was significant (F(1,14) = 15.82, P<0.005). It also indicated that both groups were able to learn the response to escape the shocks, since there was a significant difference along the trials (F(5,70) = 5.549, P<0.005), and no significant interaction between shock treatment and trial (F(5,70) = 0.9366, P>0.250). On the other hand, rats treated with either IPS or BAY showed no significant difference in the ability to escape from the shocks when compared to rats which were not exposed to uncontrollable shocks, but which received the same drug treatment (F(1,14) = 0.8038, P>0.250 and F(1,14) = 3.003, P>0.100, respectively), as shown in panels B and C of Figure 1. Ipsapirone-treated rats were able to learn the escape response, since there was a significant difference along the trials (F(5,70) = 10.03, P<0.005) and no significant interaction between shocks and trials (F(5,70) = 0.5449, P>0.250). The same applied to BAY-treated rats, which also showed a significant difference along trials (F(5,70) = 9.465, P<0.005) and no significant interaction between shocks and trials (F(5,70) = 0.4414, P>0.250).

These results clearly show that subchronic administration of either a partial (IPS)
Figure 1 - Effect of the 5-HT$_{1A}$ receptor agonists ipsapirone and BAY R 1531 on the ability of male rats to escape from shock in a shuttlebox. The drugs were administered ip for five consecutive days as described in the text to rats previously submitted (-----) or not (——) to a shock session. A, Control group which received distilled water; B, ipsapirone (13 mg/kg, daily); C, BAY R 1531 (0.375 mg/kg, daily). Each group consisted of 8 rats. Each point in the figure is the mean escape latency in seconds for a block of five trials.

or a full (BAY) 5-HT$_{1A}$ receptor agonist reversed the learning deficit caused by uncontrollable shocks, an effect characteristic of antidepressant drugs (4). Similar findings have been recently reported by Giral et al. (5) with several 5-HT$_{1A}$ receptor ligands including IPS. Nevertheless, in the latter study the effective daily dose of IPS (0.06 mg/kg) was nearly 150 times lower than that used in the present experiments, indicating that IPS causes a selective effect on escape in the learned helplessness test within a wide range of doses. Together with previously reported data (6,7), the antidepressant-like action of 5-HT$_{1A}$ agonists supports the importance of studying the role of 5-HT$_{1A}$ receptors in depressive disorders.

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References


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