Hypotensive Spinal Serotonergic Effect
Are S₁ or S₂ Receptors Involved?

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SUMMARY Since previous data obtained in anesthetized rats supported the idea that the activation of spinal serotonergic receptors induced a hypotensive effect, it was decided to characterize more closely the serotonergic spinal involvement and to elucidate the serotonergic receptor type involved in this effect. After female Wistar rats were anesthetized, the femoral artery (for blood pressure measurement) and vein (for parenteral injection of drugs) were cannulated. An intrathecal catheter was positioned with the tip at the T6-L3 intervertebral space. The results showed that the dose-dependent decrease in mean blood pressure induced by serotonin administered at the T6-L3 level was prevented by giving the serotonergic S₂ antagonist ritanserin intravenously. The intravenous administration of 5-methoxy-N,N-dimethyltryptamine, a direct serotonergic agonist, induced a dose-dependent hypotension previously shown to originate at spinal cord level. This effect was prevented by intrathecal administration of ketanserin, an S₁-receptor antagonist. The selective agonist of the S₁-type receptors, 8-hydroxy-dipropylaminotetralin, given at the same level of the spinal cord, failed to induce any effect on mean blood pressure. The results suggest that the hypotensive effect obtained after the spinal serotonergic activation involves serotonin receptors of the S₂ type.

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KEY WORDS • serotonin • blood pressure control • S₂ antagonists • spinal cord

It is known that the central serotonergic system is involved in blood pressure (BP) regulation. However, the exact role played by the bulbospinal serotonergic pathways in this regulatory system is not yet clarified. In attempting to elucidate this role, we showed in anesthetized rats that the spinal serotonergic receptors can, when activated either by serotonin or by a direct serotonergic agonist, 5-methoxy-N,N-dimethyltryptamine (5-MeODMT), induce a decrease in mean blood pressure. The aim of the present work was to identify the nature of the serotonergic receptors involved in this hypotensive action.

Materials and Methods
Female Wistar rats weighing 180 to 250 g were used. On the day of the experiment they were anesthetized with urethane (1.2 g/kg i.p.) and both femoral artery and vein were cannulated. BP was measured by connecting the arterial cannula to a Statham P23ID transducer (Hato Rey, Puerto Rico) and recorded by using a Grass 79D polygraph (Quincy, MA, USA). The femoral vein catheter was used for intravenous drug injection and the administration rate was always 0.1 ml/min.

After that, while recording BP, a cannula was positioned at the T6-L3 intervertebral space as described by Bassam. Briefly, the animals were placed in the ventral decubitus position. Once the space between the last cervical and the first thoracic vertebrae was reached, a cannula (outside diameter, 0.65 mm) was gently pushed downward 4.5 cm. The catheter was anchored to the T1 processus transversus and the skin sutured. The cannula position was verified postmortem by ventrally opening the vertebrae and localizing the cannula tip. Animals with cardiovascular or respiratory alterations after intrathecal cannulation or in which the tip was incorrectly positioned were not included in the study.

The intrathecal drug administration was always done at a rate not greater than 1 µl/min by using a 5-µl Hamilton microsyringe. Before starting with the experiments, 30 minutes were always allowed for the cardiovascular parameters being studied (BP and heart rate) to stabilize.

Four animals received serotonin, 1.5, 3, and 4.5 µg intrathecally. When BP returned to basal values, ritanserin, 0.5 mg/kg i.v., was given, and after 5 minutes serotonin, 1.5, 3, 4.5, and 6 µg, was repeated. Three animals received 5-MeODMT, 0.03, 0.1, and 0.3 mg/kg i.v. After BP returned to basal values, ketan-
serotonin, 1 μg, was intrathecally administered, and after 5 minutes 5-MeODMT, 0.03, 0.1, 0.3, and 1 mg/kg i.v., was given. Four animals received 8-hydroxy-dipropylaminotetralin (8-OHDPAT) intrathecally in doses ranging from 1 to 6 μg. In each one of the animals studied, vehicle (saline solution) was given by the same route and in a volume similar to that of the agonist. Each experiment lasted not longer than 4.5 hours.

The following drugs were used. 1) Direct serotoninergic S₁ and S₂ agonists: serotonin, creatinine sulfate, and 5-MeODMT crystalline (Sigma Chemical, St. Louis, MO, USA). 2) Direct S₁-receptor agonist: 8-OHDPAT hydrobromide (Research Biochemicals, Wayland, MA, USA). 3) Specific S₂ serotoninergic antagonists: ketanserin tartrate and ritanserin tartrate (Janssen Pharmaceutica, Beerse, Belgium).

All the doses reported refer to the concentration of the base of the compound. All values reported represent means ± SEM. The statistical significance of differences between groups was calculated by means of the Student’s t test for unpaired data. A p<0.05 was considered significant.

Results
Concentrations of serotonin that normally do not cross the blood-brain barrier (1.5, 3, and 4.5 μg) when given intrathecally at the T6-L3 level induced a dose-dependent decrease in mean BP (Figure 1). A similar dose-dependent hypotensive effect was obtained after giving 5-MeODMT (0.03, 0.1, and 0.3 mg/kg i.v.), a serotoninergic agonist that easily crosses the blood-brain barrier (Figure 2). When the selective serotoninergic S₁-receptor agonist 8-OHDPAT was intrathecally injected in doses ranging from 1 to 6 μg, no effect on BP was observed (see Figure 1).

The serotonin hypotensive effect was prevented by pretreating the animals with ritanserin (0.5 mg/kg i.v.) (Figure 3). In these animals the basal mean BP (70.2 ± 5.9 mm Hg) was unaltered by the administration of ritanserin (72.8 ± 9.9 mm Hg).

To verify the spinal origin of the hypotensive ac-
tion of 5-MeODMT, ketanserine, 1 μg, was administered intrathecally 5 minutes before the serotonergic agonist. The basal mean BP (70.8 ± 2.5 mm Hg) was significantly reduced after giving ketanserin (57.8 ± 3.6 mm Hg). As shown in Figure 2, this S₂ antagonist significantly prevented the hypotensive action of the agonist.

Discussion

Our results showed that spinal serotonergic activation induced a dose-dependent decrease in mean BP. This effect seems to be mediated by serotonergic S₂-type receptors.

Different authors previously showed that bulbo-spinal serotonergic activation is able to induce either a hypotensive⁶-⁹ or a hypertensive effect.¹⁰-¹² This discrepancy may be explained by the fact that in several of these works supporting a hypertensive action, the results were obtained in animals in which selective electrical stimulation of raphe nuclei ventrolaterally localized in the medulla oblongata was carried out.¹⁰,¹¹ Our results were always obtained in animals in which the central serotonergic activation was induced by stimulating all the serotonergic receptors (5-MeODMT, i.v.), whether localized at the cephalic or caudal area. Moreover, since the response obtained was always a reduction in BP, either in anesthetized (References 2 and 3, and present data) or conscious rats (data not shown), and as this action was either increased or prevented by selectively destroying spinal serotonergic²,³ or catecholaminergic terminals,⁷ we thought that this hypotensive action could be explained by an interaction with the activity of the final neural efferent common pathway; that is, with the preganglionic sympathetic neurons. This hypothesis was partly verified, since the selective activation of serotonergic receptors produced by giving serotonin at the thoracolumbar level, the origin of the sympathetic preganglionic nerves, induced a hypotensive effect. These results are in accordance with others previously reported, suggesting that a decrease in preganglionic activity is obtained by a serotonergic effect at the spinal cord level.⁶-⁹

Next, it was necessary to identify the subtype of serotonergic receptor involved in this effect, since two major populations, S₁ and S₂, were reported¹³ as being widely distributed at central and peripheral levels. However, evidence concerning the relationship between central cardiovascular control and these receptor subtypes is lacking. Recently, Dalton¹⁴ reported that in conscious rats receiving serotonin intracerebroventricularly, an S₁ receptor could be involved in controlling heart rate. Moreover, an S₂-receptor subtype seems to be involved in the delayed hypotensive effect that originates in brainstem areas,¹⁵ since it was prevented by cyproheptadine.

In our work, the hypotension obtained by directly injecting serotonin at the thoracolumbar level or by activating central serotonergic receptors (5-MeODMT, i.v.) was significantly prevented by pretreating the animals with selective S₂-receptor antagonists ketanserin and ritanserin. This evidence indicating an S₂ spinal involvement is further supported by the fact that selective S₁ activation at the same spinal level mentioned above (8-OHDPAT) failed to induce any effect on BP.

In conclusion, the results reported here support the idea that serotonergic receptors localized at the thoracolumbar spinal level are able, when activated, to induce a decrease in blood pressure. These receptors seem to be of the S₂ type.

References

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