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Nonserotonergic Control of Nucleus Accumbens Dopamine Metabolism by the Median Raphe Nucleus

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WIRTSHAFTER, D. AND R. TRIFUNOVIC. *Nonserotonergic control of nucleus accumbens dopamine metabolism by the median raphe nucleus.* PHARMACOL BIOCHEM BEHAV **41**(3) 501–505, 1992.—Injections of the GABA agonist muscimol into the median raphe nucleus (MR) have been shown to result in an acceleration of dopamine metabolism within the nucleus accumbens. To examine whether serotonergic mechanisms play a role in this effect, muscimol or its vehicle was injected into the MR of either control subjects or of rats that had received prior injections of the serotonin-depleting agent *p*-chlorophenylalanine (PCPA). Although PCPA treatments produced massive depletions of forebrain serotonin, they failed to alter the effect of muscimol infusions on dopamine metabolism. This finding suggests that the effects of intra-MR injections of muscimol on accumbens dopamine turnover do not result entirely from an interaction between serotonergic and dopaminergic systems.

Median raphe nucleus GABA Muscimol Serotonin Dopamine Nucleus accumbens Hyperactivity

IT has been well established that the median raphe nucleus (MR) is one of the major sources of serotonergic projections to the forebrain (31). Several recent studies have demonstrated that microinjections of the $GABA_A$ agonist muscimol into the MR result in a reduction in serotonin metabolism or release within the hippocampus and several other brain structures (14,34,46). Intra-MR injections of muscimol also result in pronounced locomotor hyperactivity (35,38,44–46) and in an increase in dopamine metabolism within the nucleus accumbens (33,46). To correctly interpret these results, it is important to examine the extent to which these three effects are independent of each other. For example, muscimol-induced hyperactivity is exceptionally resistant to blockade by dopamine antagonists, suggesting that it does not result entirely from an acceleration of dopamine release within the nucleus accumbens (46). In addition, the hyperactivity produced by muscimol injections does not appear to result entirely from an inhibition of serotonergic neurons since it persists in animals with massive depletions of serotonin (35,45). Although this result might seem surprising, it should be remembered that both the dorsal raphe nucleus (DR) and the MR contain large populations of nonserotonergic cells (12,28,31). In the MR, nonserotonergic cells constitute a majority of the total cell population (31). A large number of studies have now shown that many of the dramatic behavioral effects seen after manipulations of the MR or DR appear to be mediated primarily by nonserotonergic cells (3–5,16,21,27,29,47).

In contrast to the questions discussed above, nothing is known about the extent to which the increase in accumbens dopamine metabolism produced by intra-MR injections of muscimol is secondary to the suppression of serotonin release produced by these injections. This problem is, perhaps, of special interest since many authors have speculated on the occurrence of some type of interaction between central serotonin and dopamine systems and a substantial number of studies have demonstrated alterations in dopaminergic parameters following a variety of manipulations of the midbrain raphe nuclei (6,8,10,11,15,18,19,24,32,37–39,42,48). In addition, a rich serotonergic innervation is present in the ventral tegmental area and the substantia nigra, from which most ascending dopamine projections to the forebrain arise, and electrophysiological studies have demonstrated that the firing rate of dopaminergic cells can be altered by serotonergic manipulations (13,17). The discussion of the previous paragraph, however, suggests that considerable caution should be exercised before concluding that the effects of manipulations of the

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midbrain raphe nuclei result entirely from an effect on serotonergic systems. An additional interpretive difficulty arises from the fact that raphe manipulations result in a number of behavioral effects, such as alternations in activity and food intake (2,3,27,29,47), that might, by themselves, be expected to alter dopamine metabolism.

One method for investigating the involvement of serotonergic mechanisms in the effects produced by intra-MR drug injections is to examine whether these effects are altered in animals with large depletions of serotonin. It has been found, for example, that serotonin depletion is able to block the hyperactivity induced by intra-MR injections of tachykinin agonists (35) and of the serotonin-1A agonist 8-OHDPAT (in preparation). In the current study, we utilized this methodology by examining whether the increase in dopamine metabolism in the nucleus accumbens produced by intra-MR injections of muscimol can be altered by pretreatment with the serotonin synthesis inhibitor *p*-chlorophenylalanine (PCPA).

METHOD

Subjects were 31 male Sprague-Dawley-derived rats obtained from a colony maintained by the University of Illinois at Chicago. Subjects weighed between 275–325 g at the time of surgery. Under sodium pentobarbital anesthesia (50 mg/kg), rats were prepared with chronically implanted 22-ga stainless steel guide cannulae terminating 2 mm dorsal to the MR. The cannulae were attached to the skull with dental cement and 28-ga stainless steel obturators were inserted into them following surgery.

Locomotor activity was measured in one of four identical infrared photocell boxes measuring 71.5 × 71.5 × 27 cm. The boxes were painted black and lighting was provided by overhead fluorescent fixtures. Beam interruptions were recorded in 4-min time bins on counters located in another room.

Animals were allowed 7–10 days to recover from surgery, at which time they were randomly divided into PCPA (n = 16) and vehicle (n = 15) groups. PCPA was suspended in 2% Tween-80 and injected IP at a concentration of 100 mg/ml. Rats received two injections of PCPA (300 mg/kg) or its vehicle with 1-day intervening between them. Two days following the second treatment, rats received intra-MR injections of either muscimol (100 ng) or its isotonic saline vehicle, resulting in four experimental groups: no PCPA/saline (n = 9), no PCPA/muscimol (n = 6), PCPA/saline (n = 8), and PCPA/muscimol (n = 8). Injections were made in a volume of 0.5 μl infused over a period of 2 min through a 28-ga injection cannula connected to a motor-driven Hamilton microsyringe. The injectors were constructed so as to extend 2 mm beyond the end of the guide cannulae. The injection cannulae were kept in place for 30 s following completion of the injections, at which time they were removed and the obturators replaced. Animals were then individually placed in the activity boxes for a period of 60 min, after which subjects were sacrificed by cervical fracture and their brains quickly removed. The brainstems were placed in formalin to allow for later histological analysis and the hippocampi were dissected out on an ice-cold glass plate. Samples of the nucleus accumbens were removed using the tissue punch technique as described in detail elsewhere (45). Tissue samples were homogenized in mobile phase (26) and then centrifuged. The supernatants were stored at −70°C until they were assayed by HPLC (26). Protein content of the pellets was measured by the method of Lowry (30). The technique utilized allowed for the measurement of dopamine (DA), serotonin (5-HT), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA). Ratios of metabolites to the parent transmitter were used as indicators of transmitter metabolism (41).

Data were examined statistically by analysis of variance (ANOVA). When significant interactions were obtained, simple main effects were examined by means of single *df* contrasts.

RESULTS

Histological examination revealed that all the injection cannulae terminated within the MR at sites similar to those documented in previous studies (44–48). Most of the cannulae were located in the dorsal portion of the MR at the anteroposterior level of Gudden's ventral tegmental nuclei.

Behavioral results are shown in Fig. 1, where it can be seen that muscimol injections resulted in a large increase in locomotor activity. Analysis of total activity counts by means of a 2 × 2 factorial ANOVA indicated both a significant effect of muscimol treatment, $F(1,27) = 70.71$, $p < 0.001$, and a significant muscimol × PCPA interaction, $F(1,27) = 14.66$, $p < 0.01$. Analysis of simple main effects indicated that PCPA pretreatment significantly potentiated the locomotor response to muscimol injections, $F(1,27) = 15.90$, $p < 0.01$, but failed to alter the response to saline injections, $F(1,27) = 1.61$, $p > 0.2$.

Effects of PCPA and intra-MR muscimol injections on levels of serotonin and 5-HIAA are shown in Table 1. PCPA injections resulted in massive depletions of both serotonin and 5-HIAA in both regions studied ($p < 0.001$); 5-HIAA was undetectable in the majority of animals treated with PCPA. In subjects not receiving PCPA, muscimol injections produced a significant decrease in levels of 5-HIAA and in the 5-HIAA/5-HT ratio in both the hippocampus and accumbens ($p < 0.05$).

Dopamine metabolite ratios in the nucleus accumbens are shown in Fig. 2, where it can be seen that, while PCPA treatment tended to produce a small reduction in dopamine metabolism, muscimol injections produced a marked increase in metabolite ratios that was of almost identical magnitude in normal and PCPA-treated animals. Analysis of the

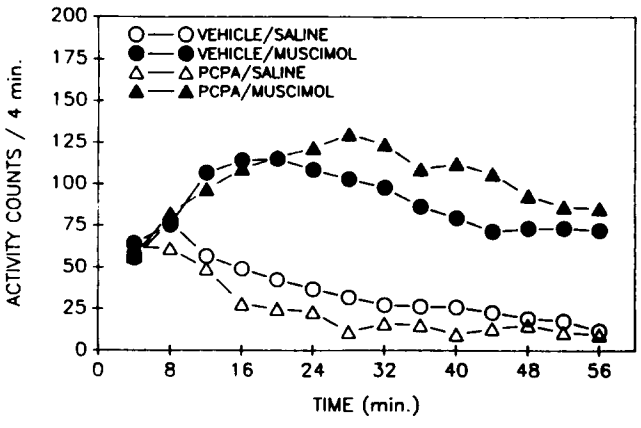

FIG. 1. Photocell activity counts in 4-min time bins for control and PCPA-treated rats following intra-MR injections of saline or 100 ng muscimol. Samples sizes for the four groups were: vehicle/saline, n = 9; vehicle/muscimol, n = 6; PCPA/saline, n = 8; PCPA/muscimol, n = 8.

TABLE 1

EFFECTS OF PCPA AND MUSCIMOL ON SEROTONIN METABOLISM

	5-HT (ng/mg protein)	5-HIAA (ng/mg protein)	5-HIAA/5-HT
Hippocampus			
Vehicle/saline (n = 9)	4.38 ± 0.20	3.40 ± 0.16	0.800 ± 0.068
PCPA/saline (n = 6)	0.15 ± 0.02*	0.03 ± 0.01*	–†
Vehicle/muscimol (n = 8)	5.40 ± 0.39*	2.61 ± 0.30*	0.505 ± 0.071*
PCPA/muscimol (n = 8)	0.19 ± 0.03*	0.04 ± 0.01*	–†
Accumbens			
Vehicle/saline (n = 9)	5.25 ± 0.80	3.88 ± 0.81	0.751 ± 0.094
PCPA/saline (n = 6)	0.17 ± 0.06*	0.08 ± 0.01*	–†
Vehicle/muscimol (n = 8)	4.45 ± 0.66	1.76 ± 0.78*	0.406 ± 0.028*
PCPA/muscimol (n = 8)	0.59 ± 0.16*	0.16 ± 0.11*	–†

Mean ± SEM

*$p < 0.05$ vs. vehicle/saline group

†Not calculated owing to the presence of animals with undetectable levels of 5-HIAA.

DOPAC/DA ratios by means of a 2 × 2 (PCPA × muscimol) ANOVA indicated a significant effect of muscimol injections, $F(1,27) = 21.3, p < 0.001$, but not of PCPA treatment ($p > 0.08$). The PCPA × muscimol interaction also failed to approach statistical significance ($F < 1$). Analysis of HVA/DA ratios (Fig. 2B) again indicated that the muscimol effect was significant, $F(1,27) = 11.14$, $p < 0.002$, but that the PCPA ($p > 0.07$) and interaction effects ($F < 1$) were not. Examination of the raw data indicated that the effects on metabolite ratios primarily reflected increases in the levels of DOPAC and HVA, although the absolute levels of these compounds were considerably more variable than were the metabolite ratios.

DISCUSSION

The present results confirm reports of hyperactivity following intra-MR injections of muscimol (35,38,44–46). In other studies, we found that the locomotor response seen after muscimol injections in the MR is much larger than that observed after injections in the DR, the ventral tegmental area, the nucleus raphe points (44), or the reticular formation lateral to the MR (unpublished observations), suggesting that the hyperactivity does not result from diffusion of the muscimol outside the MR. In a previous study, we found that PCPA pretreatments identical to those employed here tended to increase the locomotor response to muscimol, but the effect was not statistically significant (45). In the current study, a small, but significant, potentiation of the muscimol effect was observed. These findings are in agreement with other results (35) suggesting that the occurrence of the locomotor response to muscimol injections is not critically dependent on intact serotonergic systems. In contrast, serotonin-depleting treatments have been shown to attenuate the locomotor responses to intra-MR injections of the serotonin agonist 8-OHDPAT (in preparation) and of the tachykinin agonist DiME-C7 (35), suggesting that the response to these drugs, unlike that to muscimol, is dependent upon serotonergic systems. The reason PCPA produced an actual potentiation of muscimol induced hyperactivity is unclear; it is possible that it might be related to the ability of PCPA treatments to potentiate the hyperactivity induced by drugs such as amphetamine, which do not appear to increase activity through an action on serotonergic mechanisms (22, 40).

The finding that muscimol infusions produced a decrease in serotonin metabolism within the hippocampus is also in agreement with previous studies (14,34,45) and suggests that the muscimol inhibited serotonergic cells within the MR that project to the hippocampus.

In the current study, injections of PCPA tended to reduce the DOPAC/DA and HVA/DA ratios in the nucleus accumbens, although this trend was not statistically significant. Other authors have reported that PCPA can alter forebrain dopamine levels or metabolism (25,36,39), although it is

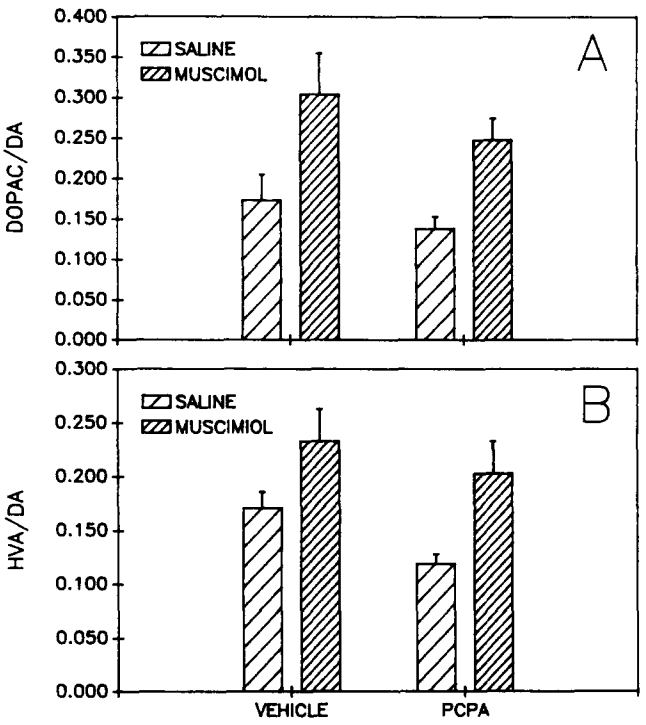

FIG. 2. Ratios of (A) DOPAC to dopamine and (B) HVA to dopamine in the nucleus accumbens of PCPA- or vehicle-treated rats sacrificed 1 h following intra-MR injections of saline or 100 ng muscimol.

uncertain whether such effects are secondary to serotonin depletion (39) or whether they reflect a nonspecific action of PCPA.

The most important result of the current study is the finding that PCPA pretreatment depleted forebrain serotonin by about 95% but failed to produce any alteration in the magnitude of the effect of muscimol infusions on dopamine metabolism in the nucleus accumbens. It is remotely possible that residual serotonin may have mediated this effect, but it should be noted that PCPA pretreatments have been found to block a number of effects produced by drug injections in the raphe nuclei [e.g., (35,42)]. It is of particular interest in the current context that PCPA has been shown to antagonize the alterations in forebrain dopamine metabolism produced by injections of morphine into the DR (42). These findings indicate that PCPA-induced depletions of serotonin are indeed able to block a number of behavioral and biochemical effects that appear to be mediated through serotonergic mechanisms. The extent to which serotonergic function can be disrupted without altering the effects of intra-MR muscimol on dopamine metabolism is certainly striking and supports the conclusion that nonserotonergic mechanisms may play an important role in this effect. This conclusion is in accord with studies, cited above, that demonstrated that nonserotonergic cells play an important role in many of the behavioral effects of MR manipulations. It should be stressed that the current results do not contradict the notion of a serotonin/dopamine interaction but merely suggest that nonserotonergic mechanisms play an important role in mediating the influence of the MR on forebrain dopamine turnover.

It is interesting to note that two recent studies reported that intra-MR injections of the serotonin autoreceptor agonist 8-OHDPAT produce a marked decrease in hippocampal serotonin synthesis without altering dopamine synthesis in the nucleus accumbens (20,23). Since serotonin agonists appear to selectively depress the firing of serotonergic cells within the raphe nuclei (1), these findings imply that acute inhibition of serotonergic neurons within the MR is not sufficient to induce alterations in forebrain dopamine metabolism. This conclusion clearly supports our current suggestion that nonserotonergic elements play an important role in mediating the effects of MR manipulations on accumbens dopamine turnover.

If the conclusion that serotonin does not play an essential role in the effects of intra-MR muscimol infusions on dopamine metabolism is correct, a number of possibilities exist that might account for this phenomenon. Since several studies have shown that forced locomotor activity can lead to changes in dopaminergic parameters (7,9,43,49), it is plausible that the hyperactivity produced by the muscimol infusions may have mediated the effects of these injections on dopamine metabolism. Another possibility is that the effects of the muscimol infusions could have been mediated through nonserotonergic projections from the MR to the ventral tegmental area. Further studies will be necessary to clarify the effects of median raphe manipulations on accumbens dopamine metabolism, but the current results serve to emphasize that neither the behavioral nor the biochemical effects produced by manipulations of the midbrain raphe nuclei can be assumed, a priori, to result from alterations in serotonergic functioning.

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