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Bilateral Neurochemical Changes Induced by Unilateral Cerebral Haloperidol Administration: Evidence for Cerebral Asymmetry in the Rat

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HYDE, J. F. AND T. P. JERUSSI. *Bilateral neurochemical changes induced by unilateral cerebral haloperidol administration: Evidence for cerebral asymmetry in the rat.* PHARMACOL BIOCHEM BEHAV 42(3) 457–464, 1992.—Bilateral alterations in dopamine metabolism were determined in the striatum, olfactory tubercle, and frontal cortex of rats pretested for circling behavior. Dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), norepinephrine, and 5-hydroxyindole-3-acetic acid (5-HIAA) were measured by high-performance liquid chromatography 15 min after right or left intracarotid infusion of haloperidol. Concentrations of DOPAC and HVA were significantly increased in the striatum and frontal cortex ipsilateral to the side of haloperidol infusion, regardless of whether it was right or left. In contrast, the concentrations of these metabolites were unchanged in the olfactory tubercle after a right side infusion, but bilateral increases were evident after a left side infusion. Higher levels of DOPAC and HVA were also apparent in the left striatum and olfactory tubercle after intravenous jugular administration of haloperidol. Dopamine levels were significantly lower in the left striatum and right olfactory tubercle after intravenous haloperidol infusions. 5-HIAA concentrations were higher in the left olfactory tubercle following left side infusions of haloperidol. These data indicate that unilateral cerebral administration of haloperidol induces asymmetric and side-dependent alterations in dopamine and serotonin metabolites. These differences appear to be due to intrinsic variations in the sensitivity to haloperidol, but are not associated with the direction of circling behavior.

Cerebral asymmetry Dopamine Haloperidol Unilateral cerebral drug administration

LATERALIZED behaviors and neurochemical asymmetries have been reported following the administration of a wide variety of drugs (8,13,15,18). However, these asymmetries have been observed after systemic drug administration in which pharmacologically active doses are delivered to both cerebral hemispheres. We recently described a procedure in which drugs infused into the internal carotid artery of conscious animals are selectively delivered to only one cerebral hemisphere (11). For example, unilateral cerebral administration of haloperidol resulted in an 80- to 90-fold right–left drug concentration difference in the forebrain structures. Unilateral cerebral drug administration should therefore be able to induce bilateral neurochemical asymmetries. Using this technique, the sensitivity of each cerebral hemisphere to drugs and interhemispheric relationships may be studied.

The extensively studied nigrostriatal dopaminergic pathways have been shown to be involved in some behavioral asymmetries (7,26). Drug-induced rotation (circling) in normal rats without lesions has been shown to be correlated to an asymmetry of dopamine (DA) in nigrostriatal neurons (14). In addition, spontaneous rotation seen during the dark phase of the diurnal cycle is associated with an asymmetry of these dopaminergic pathways (6). Therefore, circling behavior may be used as an index of cerebral asymmetry to discriminate a specific population of rats with cerebral hemispheres that respond differentially to pharmacological agents. To test this hypothesis, we investigated the bilateral neurochemical responses following intravenous or unilateral cerebral haloperidol administration in rats previously tested for circling behavior.

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METHOD

Materials

Sodium methohexital (Brevital) was purchased from Eli Lilly and Co. (Indianapolis, IN); 3,4-dihydroxyphenylacetic acid (DOPAC), 4-hydroxy-3-methoxyphenylacetic acid [homovanillic acid (HVA)], 5-hydroxyindole-3-acetic acid (5-HIAA), 3,4-dihydroxyphenylethylamine HCl (DA), norepinephrine HCl (NE), 3,4-dihydroxycinnamic (caffeic) acid, 3,4-dihydroxybenzylamine HBr (DHBA), Sephadex G-10, and heparin (grade II) were obtained from Sigma Chemical Co. (St. Louis, MO); sodium octyl sulfate was obtained from Bioanalytic Systems, Inc. (West Lafayette, IN); all other reagents were of high-performance liquid chromatography (HPLC) or analytical grade. Haloperidol was dissolved in a drop of glacial acetic acid and then diluted to the appropriate volume with saline. The vehicle, acidified saline, was prepared in an identical manner.

Animals

Female Sprague-Dawley rats (Taconic Farms, Inc., Germantown, NY) weighing approximately 225–250 g at the time of surgery were used in all experiments. Prior to surgery, rats were maintained four to five per cage on a diurnal cycle (1830–0630 h for the dark phase). Cannulated rats were maintained one per cage. Food and water were available ad lib.

Cannulation Procedures

To preferentially deliver drug to only one cerebral hemisphere, the common carotid artery was cannulated as previously described (11). Briefly, rats were anesthetized with Brevital (40 mg/kg, IP). A small incision was made on the ventral medial surface of the neck, and the right or left common carotid artery was exposed and separated from the vagus nerve. The artery was ligated proximal to the aorta using surgical silk (3-0, black-braided). The external carotid and pterygopalatine arteries were ligated to direct more of the injected drug to the brain. The common carotid artery was then cannulated rostrally using polyethylene tubing (PE50) previously filled with a heparinized saline solution (2 mg/ml). The cannula was then externalized and the incision closed. Jugular vein cannulations were performed by a similar surgical procedure. Following exposure of the right or left jugular vein, the vessel was cannulated using PE50 tubing.

Drug Infusions

All drug infusions were made into the cannulated blood vessel 1 day after surgery. The cannula was filled with 10 μl drug or vehicle, which was then infused as a bolus by attaching the cannula to a saline-filled syringe driven by a Compact Syringe Pump (Harvard Apparatus Co., Millis, MA). An infusion rate of 0.39 ml/min for 20 s (i.e., total volume injected into the cannula was 0.13 ml) was used for all infusions. Animals receiving unilateral cerebral haloperidol were infused with 1 μg. Jugular vein infusions were with 1, 2, 4, 8, 16, and 32 μg haloperidol.

Behavioral Testing

Prior to haloperidol or vehicle administration, all animals were tested for rotational (circling) behavior as previously described (10,12). Briefly, after a 15-min period of acclimation to the rotometer animals were injected with *d*-amphetamine sulfate (1.0 mg/kg, IP). Rotational behavior was then recorded for 1 h. Animals with 10 or more net rotations (i.e., rotations in the predominant direction less those in the nondominant direction) were tested a second time 1 week later. Only those animals showing the same rotational bias during the two test sessions were used in this study. Equal numbers of rats with right and left rotational biases were placed in each experimental group when possible. Animals were not cannulated until at least 1 week after the final behavioral test.

Tissue Preparation

All animals were sacrificed by decapitation 15 min after drug infusion. The brain was rapidly removed and dissected. The right and left striata (dorsal and ventral; mean wet weight 22.3 mg), olfactory tubercles (mean wet weight 3.4 mg), and frontal cortices (cortex anterior to the optic chiasm excluding nucleus accumbens; mean wet weight 123.4 mg) were weighed and then homogenized in 0.5 ml 1.0 M HCl using a Tissuemizer (setting 40 for 15 s; Tekmar Co., Cincinnati, OH). The homogenates were then centrifuged for 20 min at 30,000 × *g* (Beckman Model L Ultracentrifuge Beckman Instruments, Fullerton, CA). The supernatants were frozen at −70°C until assayed.

Neurochemical Analyses

Neurochemical determinations were performed using modifications (25) of previously described procedures. DOPAC, HVA, DA, 5-HIAA and NE concentrations were determined using an LC-154T LCEC Chromatographic System (Bioanalytical Systems, Inc., West Lafayette, IN). A C_{18} reverse-phase Biophase ODS (5 μm) colume was used. The mobile phase consisted of 0.15 M monochloroacetic acid, 0.86 mM sodium octyl sulfate, 3.5% acetonitrile, and 1.8% tetrahydrofuran, pH 3.0 (19).

Aliquots of the thawed supernatants were extracted with 2.0 ml methyl-*t*-butyl ether following addition of caffeic acid and DHBA as internal standards. The ether extract was then layered on top of a 0.25-ml aqueous solution containing 0.16 mM ascorbic acid, 0.24 M formic acid, and 0.005 M sodium phosphate (dibasic, pH 8.5). Following evaporation of the ether phase under a stream of nitrogen, 0.1 ml of the remaining aqueous phase was analyzed for DOPAC, HVA, 5-HIAA and caffeic acid. DA, NE, and DHBA remained in the aqueous phase following ether extraction and were applied to a Sephadex G-10 column prepared in a 9-in. disposable Pasteur pipette (27). The amines were then collected in 1.5 ml 0.1 M formic acid (28), and 0.1 ml was analyzed by HPLC.

The peak height ratios (peak height of catecholamine or acid metabolite/peak height of internal standard) were calculated for standards and samples, and the sample concentrations (μg/g wet weight of tissue) determined from the resulting standard curves. DOPAC, HVA, DA, and 5-HIAA concentrations were measured in the striatum, olfactory tubercle, and frontal cortex. NE concentrations were quantified only in the frontal cortex; NE levels in the striatum and olfactory tubercle were undetectable.

Statistical Analyses

Control animals were initially placed into three treatment groups: right side vehicle infused (n = 7), left side vehicle infused (n = 7), and no infusion (n = 10). Differences in treatment groups were examined using an analysis of variance (ANOVA; treatment × brain side × direction of rotation).

Right and left brain side differences in neurochemical concentrations in control animals were examined using paired *t*-tests. Data from animals receiving unilateral cerebral haloperidol (n = 10/side infused) were first compared to control animals using a four-way ANOVA (treatment × infusion side × brain side × direction of rotation) for each neurochemical in the three regions examined. Subsequently, variables failing to show significant correlations to other parameters were eliminated and a lower-order ANOVA performed on partially collapsed data. The brain side not infused (contralateral to the side of infusion) was compared to the appropriate control brain side using a nonpaired *t*-test. Data from animals receiving intravenous halperidol were analyzed using a two-way ANOVA (dose × brain side). The data were tested for homogeneity of variance prior to all analyses. Data failing to display homogeneity of variance as a result of the large unilateral neurochemical differences were logarithmically transformed and then subjected to ANOVA. All data analyzed using an ANOVA were subsequently analyzed using Duncan's multiple-range test ($p < 0.05$) where appropriate. All data are expressed as means ± SEM.

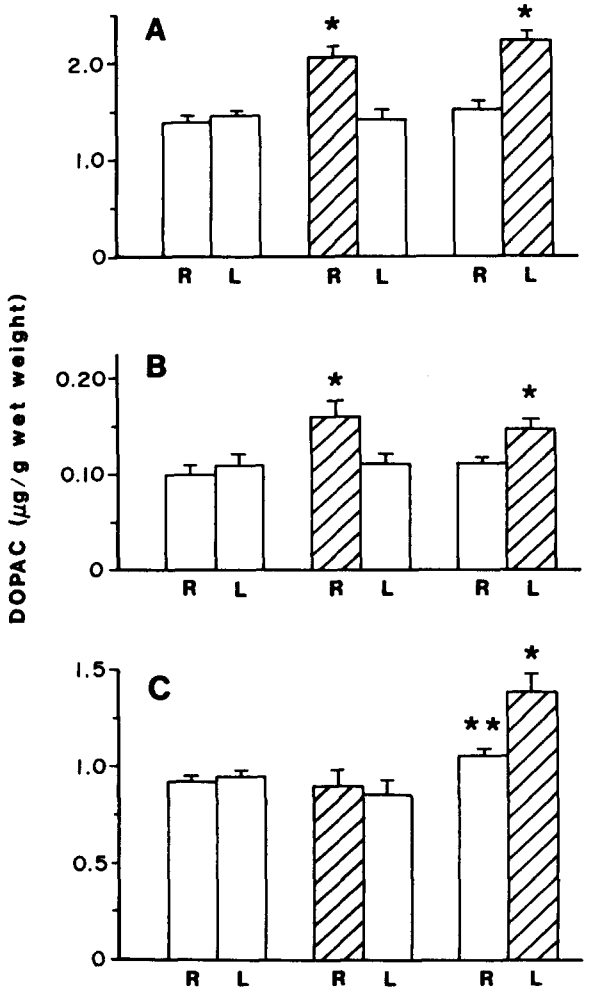

FIG. 1. Bilateral DOPAC concentrations following unilateral administration of haloperidol. Animals were infused unilaterally (n = 10/side infused) with 1 μg haloperidol and sacrificed 15 min later. DOPAC concentrations (μg DOPAC/g wet weight) were determined in the right (R) and left (L) striatum (A), frontal cortex (B), and olfactory tubercle (C). Hatched bars represent the brain side infused with haloperidol. Control animals are represented by the data in the far left pair of open bars. Each value represents the mean ± SE. *Significantly ($p < 0.05$) greater than a) the contralateral brain side and b) the ipsilateral control value. **Significantly greater than the ipsilateral control value ($p < 0.05$, *t*-test).

RESULTS

A three-way ANOVA (treatment × brain side × direction of rotation) of the control animals showed that there were no significant ($p > 0.1$) neurochemical differences between the vehicle-infused or noninfused treatment groups. No effect of the direction of rotation was observed in control animals ($p > 0.2$). In addition, there were no significant neurochemical differences between these treatment groups and animals infused intravenously via the jugular vein with 1 μg haloperidol (n = 8). The data from vehicle-infused and noninfused groups were combined (n = 24) and compared to those animals unilaterally (1 μg) or intravenously (1-32 μg) infused with haloperidol. There was a significant ($p < 0.05$) effect of brain side in the olfactory tubercle of all control animals; 5-HIAA concentrations were higher in the left (0.80 ± 0.03 μg/g wet weight) than in the right (0.73 ± 0.02 μg/g wet weight) olfactory tubercle.

A significant effect of the direction of rotation was not observed in any region in haloperidol-infused animals. The unilateral neurochemical changes observed in this study were evident in all animals, regardless of the direction of rotation, and therefore the data from right- and left-rotating animals were combined. Figure 1 shows the bilateral effects of a unilateral infusion of haloperidol on DOPAC concentrations. Significant *unilateral* elevations of DOPAC concentrations in both the striatum (Fig. 1A) and frontal cortex (Fig. 1B) were evident following either right or left carotid infusions of haloperidol. DOPAC levels were selectively increased ipsilateral to the side of the infusion in these two regions. In contrast, DOPAC levels in the olfactory tubercle (Fig. 1C) were elevated *bilaterally* after a left carotid infusion and were unchanged following a right side infusion. Significant brain side × infusion side interactions were evident in all three brain regions ($F \geq 7.5$). This interaction shows that when significant unilateral increases in DOPAC occurred they were associated with the side infused (i.e., following a right side infusion DOPAC levels were elevated in the right cerebral hemisphere). A three-way ANOVA showed a significant ($p < 0.05$) effect of the brain side infused in the olfactory tubercle; higher DOPAC concentrations were only evident following a left side haloperidol infusion.

Similar to DOPAC levels, the striatum (Fig. 2A) and frontal cortex (Fig. 2B) did show selective elevations of HVA. However, a right side infusion of haloperidol did not elevate HVA concentrations in the right or left olfactory tubercle (see Fig. 2C). Significant brain side × infusion side interactions were observed in all three brain regions, $F \geq 8.8$, $p < 0.05$. Ipsilateral HVA concentrations were significantly increased in all three regions following left side drug infusions. Moreover, both the ipsilateral and contralateral olfactory tubercle and striatum had significantly higher HVA concentrations following unilateral haloperidol infusion as compared to controls (see Fig. 2).

As shown in Fig. 3, significant effects of the side infused on DA concentrations were seen in both the striatum and olfactory tubercle. The right and left striatum and right olfactory tubercle of the right-infused animals had reduced DA

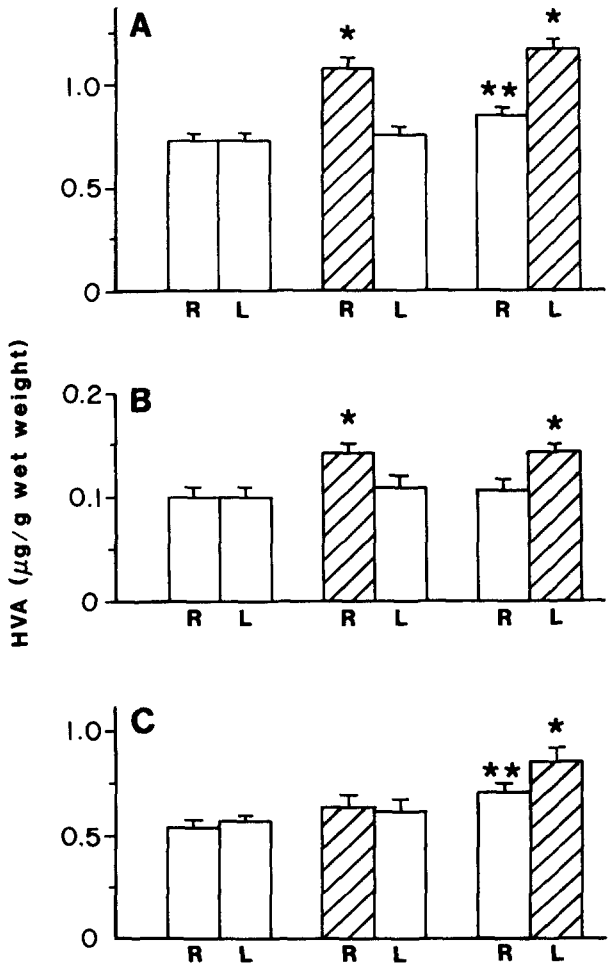

FIG. 2. Bilateral HVA concentrations following unilateral administration of haloperidol. See Fig. 1 legend for details.

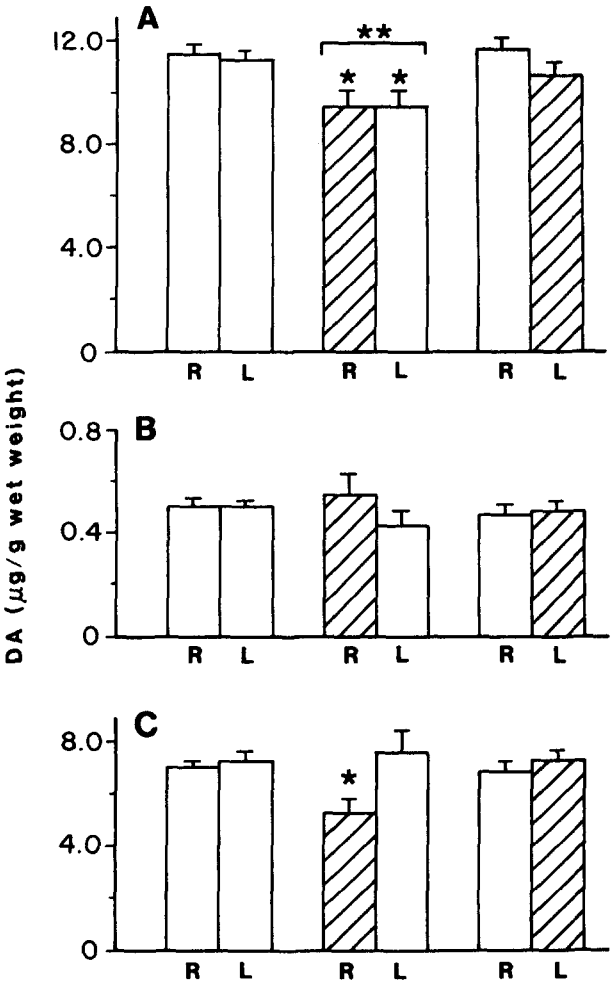

FIG. 3. Bilateral DA concentrations following unilateral administration of haloperidol. See Fig. 1 legend for details. *Significantly ($p < 0.05$) lower than the ipsilateral control values. **Significantly ($p < 0.05$) lower than left-infused or control animals.

levels compared to the left-infused and control animals. DA concentrations did not change in the frontal cortex following unilateral infusion of haloperidol.

A significant ($p < 0.05$) effect of the infusion side on 5-HIAA concentrations in only the olfactory tubercle was observed. 5-HIAA levels were significantly higher following left side infusions (0.78 ± 0.04 μg/g wet weight) compared to right side infusions (0.65 ± 0.05 μg/g wet weight). Two-way ANOVA (brain side × treatment) of haloperidol-infused and control animals indicated a significant main effect of brain side in the olfactory tubercle ($p < 0.01$), the left side having higher 5-HIAA concentrations. This asymmetry was seen previously when analyzing only control animals. No significant unilateral changes in NE concentrations in the frontal cortex were observed following intracarotid infusion of haloperidol (data not shown).

The bilateral changes of DOPAC concentrations in the striatum (Fig. 4), olfactory tubercle (Fig. 5), and frontal cortex were also measured following intravenous infusion of 1, 2, 4, 8, 16, and 32 μg haloperidol into the jugular vein. The neurochemical changes observed were identical after either right or left side jugular infusions. A significant ($p < 0.001$) effect of dose was observed in the striatum, olfactory tubercle, and frontal cortex. In all three regions, 4 μg haloperidol was the first dose to significantly elevate DOPAC levels. Moreover, the maximal elevations of DOPAC (expressed as mean percent of control) were similar in the striatum (175%), olfactory tubercle (173%), and frontal cortex (180%). A significant ($p < 0.05$) effect of brain side was also evident in the striatum and olfactory tubercle, but not in the frontal cortex ($p > 0.05$). The DOPAC levels in the left striatum and olfactory tubercle were higher. However, a dose × brain side interaction was only significant in the olfactory tubercle, $F = 2.85$, $p < 0.05$ (Fig. 5).

Similar to DOPAC, HVA concentrations increased in all three regions in a dose-dependent manner ($p < 0.001$) following the intravenous jugular infusion of haloperidol (data not shown). The first doses to significantly elevate HVA levels in the striatum, olfactory tubercle, and frontal cortex were 4, 2, and 8 μg haloperidol, respectively. The maximal elevations of HVA (% control) seen in the striatum (170%), olfactory tubercle (168%), and frontal cortex (172%) were similar to

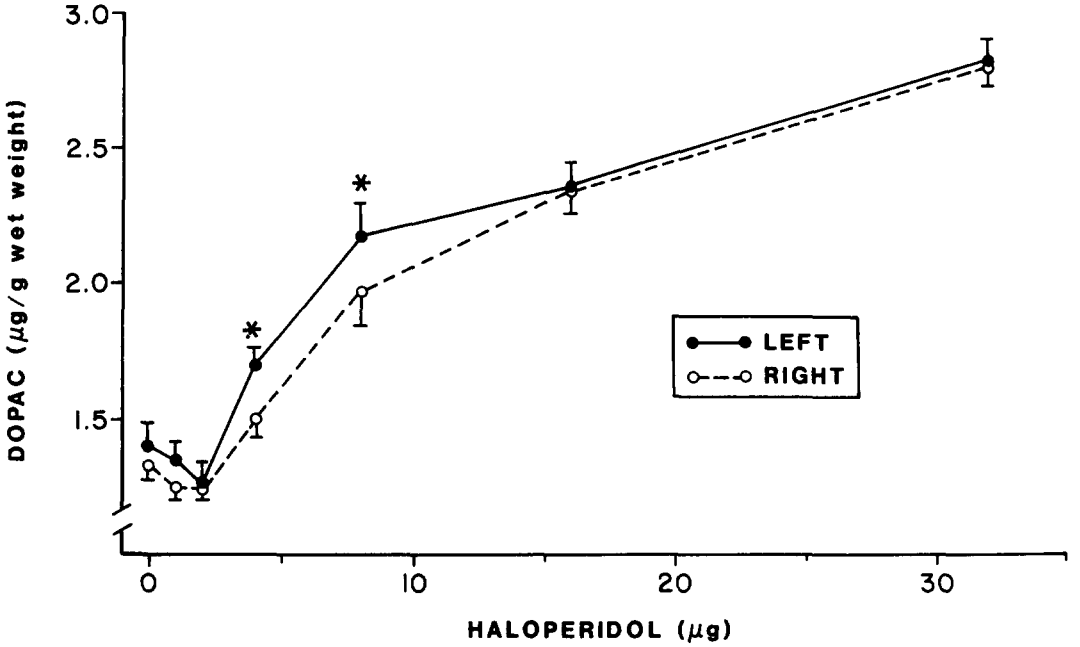

FIG. 4. Bilateral DOPAC concentrations in the striatum following intravenous administration of haloperidol. Animals (n = 7–9/dose) were infused with haloperidol (1–32 μg) via jugular cannulae. Animals were sacrificed 15 min later and bilateral concentrations of DOPAC were determined. Values are means ± SE. *Significantly ($p < 0.05$) greater than the contralateral brain side.

those previously shown for DOPAC. A significant ($p < 0.05$) effect of brain side was only evident in the olfactory tubercle; the left side had higher concentrations of HVA than the right.

Unlike DOPAC and HVA, DA concentrations did not change in a dose-dependent manner following intravenous jugular infusion of haloperidol. A significant effect of brain side was evident in both the olfactory tubercle (Fig. 6) and striatum (Fig. 7). This effect was due to an asymmetrical decline of DA levels; the left striatum and right olfactory tubercle had lower concentrations of DA. No significant effects of dose were apparent for 5-HIAA or NE concentrations in any brain region after intravenous haloperidol administration.

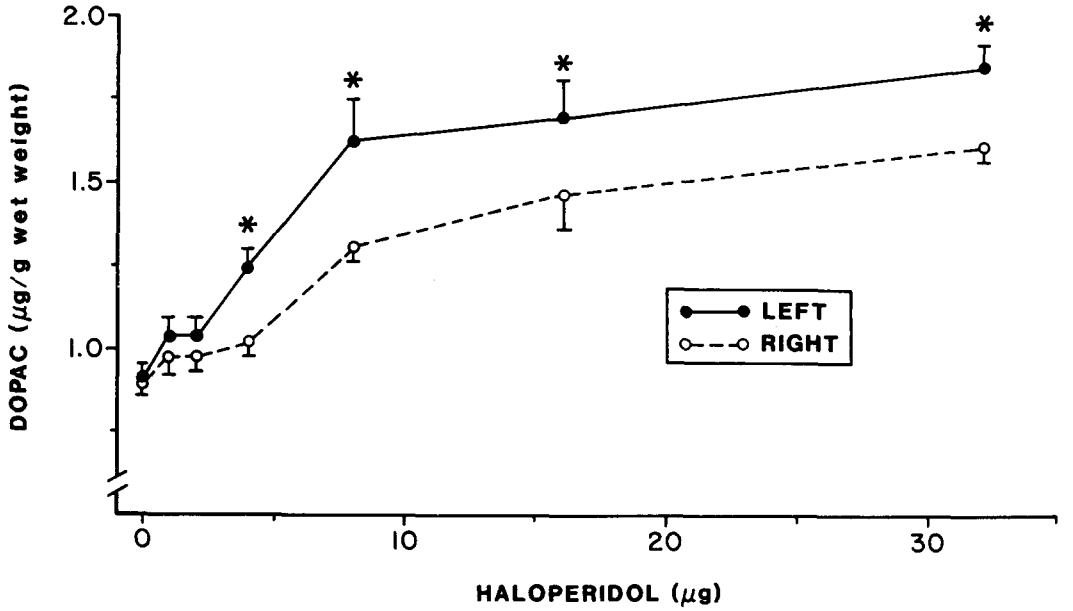

FIG. 5. Bilateral DOPAC concentrations in the olfactory tubercle following intravenous administration of haloperidol. See Fig. 4 legend for details.

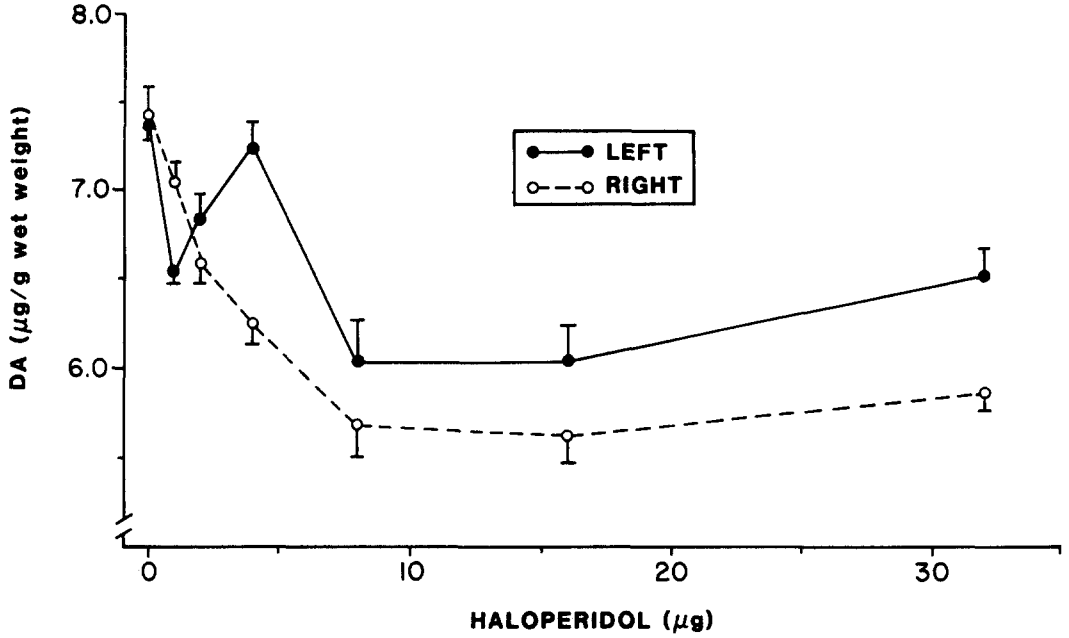

FIG. 6. Bilateral DA concentrations in the olfactory tubercle following intravenous administration of haloperidol. See Fig. 4 legend for details.

DISCUSSION

Drugs infused into the internal carotid artery are selectively delivered to the ipsilateral hemisphere because of the unilateral course of each carotid artery. Much lower levels of drug are delivered to the contralateral hemisphere due to dilution in the peripheral plasma (11). Therefore, we hypothesized that neurochemical asymmetries could be induced after intracarotid infusion of drugs. Indeed, infusion of haloperidol into the right or left carotid artery selectively increased DOPAC and HVA in the ipsilateral striatum and frontal cortex. Moreover, following infusion into the left carotid artery significant increases in HVA concentrations in the *contralateral* striatum were also evident. HVA and DOPAC concentrations in both olfactory tubercles were altered only after infusion of haloper-

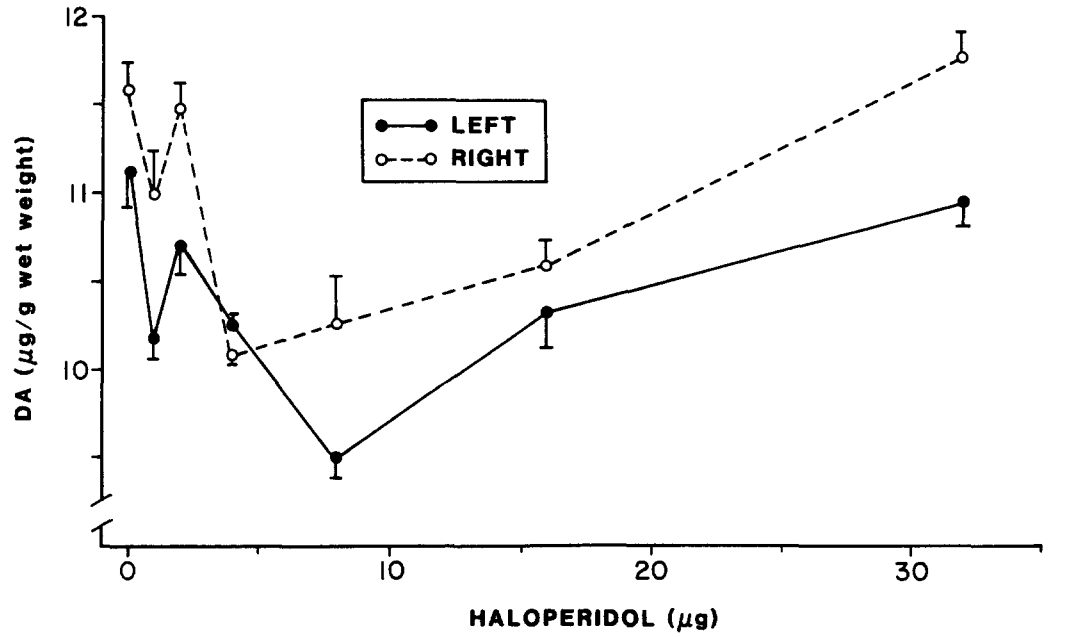

FIG. 7. Bilateral DA concentrations in the striatum following intravenous administration of haloperidol. See Fig. 4 legend for details.

idol into the left carotid artery. On the other hand, DA concentrations decreased bilaterally in the striatum and unilaterally in the olfactory tubercle following a right side infusion and were unchanged after left side infusions. These data suggest that a) the left olfactory tubercle is intrinsically more sensitive than the right to the haloperidol-induced increases in DA metabolite concentrations and b) one side of the brain can "direct" the neurochemical changes of the other side.

The neurochemical changes observed contralateral to the side of haloperidol infusion are unlikely the result of any direct action of haloperidol. Intravenous infusion of 1 μg haloperidol should mimic the plasma concentrations of drugs after intracarotid infusion of the same dose of haloperidol. In the present study, intravenous infusion of 1 μg haloperidol did not induce any neurochemical changes in the brain structures studied. Thus, the neurochemical changes observed contralateral to the infusion side are likely due to interhemispheric mechanisms.

Following unilateral intracarotid administration of haloperidol, the magnitude of the elevated ipsilateral DOPAC and HVA concentrations are consistent with the increases observed following systemic administration. However, DOPAC and HVA levels were also increased in some contralateral structures following intracarotid infusion. Nieoullon and coworkers studied the release of [^{3}H]DA in the caudate nuclei of the anesthetized cat. After manipulations in one substantia nigra, increases in the release of DA in one striatum corresponded to decreases in release of DA in the contralateral striatum (21). For example, the local application of haloperidol in one substantia nigra resulted in an increase of DA release in the ipsilateral striatum, as well as a decrease of DA release in the contralateral striatum (22). These bilateral changes were found to be associated with asymmetric changes in the dendritic release of DA in both substantia nigra in an opposite direction to those changes observed in the striata (17). Therefore, the two nigrostriatal dopaminergic pathways appear to be functionally linked and reciprocally controlled. This is also supported neuroanatomically (3-5,20,23).

In the present studies, HVA levels increased in the right and left striata following infusion of haloperidol into the left carotid artery. These bilateral changes are suggestive of interhemispheric communication. Both local and feedback mechanisms must be considered when explaining these changes. Following unilateral cerebral administration of haloperidol, concentrations of DOPAC and HVA were increased in most of the ipsilateral forebrain regions. In the ipsilateral striatum, haloperidol would block nerve terminal DA autoreceptors, and the expected result would be an increase in DA synthesis and release (16), concomitant with increases in the concentrations of DOPAC and HVA. However, the blockade of postsynaptic DA receptors in the ipsilateral striatum by haloperidol would increase the activity of the GABAergic striatonigral pathway to inhibit the dopaminergic cells of the pars compacta (24). It also has been postulated that in some instances GABAergic interneurons in the substantia nigra may be responsible for an indirect activation of the nigrostriatal pathway (9). In the present study, DA release increased in the ipsilateral striatum following unilateral intracarotid infusion of haloperidol; however, postsynaptic blockade by haloperidol would antagonize any receptor-mediated effects of DA; the effect of synaptic DA would be blocked and functionally DA release would appear to have decreased on the side of the infusion. Thus, the increased concentrations of DOPAC and HVA in the contralateral striatum after infusion of haloperidol corresponds to Nieoullon et al.'s work—when DA release is functionally decreased in one striatum, DA release in the contralateral striatum is increased.

Concentrations of DOPAC and HVA in the olfactory tubercle were increased ipsilaterally and also contralaterally only when haloperidol was infused into the *left* carotid artery. The functional implications of this observation are not apparent. Although the right olfactory tubercle appears less sensitive than the left, it is not insensitive to haloperidol; after intravenous administration of haloperidol, the right olfactory tubercle showed significant increases in DOPAC and HVA concentrations, but these increases were significantly lower than those observed on the left side.

The failure to find significant effects of the direction of circling behavior in these studies suggests that cerebral laterality, based upon the direction of rotation, does not predispose rats to consistent and predictable asymmetries of neurochemical concentrations in the regions examined after unilateral haloperidol administration. Recently, investigators correlated several measures of postural/motor asymmetries with the lateralization of DA in the brains (1). They also concluded that a "cerebral asymmetry" could not be established using a single behavioral test as the means to establish sidedness. Moreover, extracellular single-unit recordings obtained during circling behavior have shown that the firing of DA cells in the substantia nigra increases bilaterally during the initiation and maintenance of rotation behavior, and no laterality in the firing of DA neurons was observed (2).

In summary, we have demonstrated that unilateral cerebral administration of haloperidol increases metabolites of DA in the ipsilateral striatum and frontal cortex, regardless of the side infused. However, the levels of these metabolites were not changed in the olfactory tubercle after an infusion into the right carotid artery. Moreover, *bilateral* increases of DOPAC and HVA were apparent in the olfactory tubercle after a left side infusion. Higher concentrations of DOPAC and HVA were also evident in the left striatum and olfactory tubercle after intravenous administration of haloperidol. These results suggest that the left striatum and olfactory tubercle are intrinsically more sensitive than the right to the haloperidol-induced increases of DA metabolites, and that the infused hemisphere may alter neuronal activity in the contralateral hemisphere as assessed by neurochemical indices.

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