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Hypophysectomy-Induced Striatal Hypersensitivity and Mesolimbic Hyposensitivity to Apomorphine

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GORDON, J. H. *Hypophysectomy-induced striatal hypersensitivity and mesolimbic hyposensitivity to apomorphine.* PHARMACOL BIOCHEM BEHAV **19**(5) 807–811, 1983.—Seven days post-hypophysectomy female rats display a hyposensitivity to the locomotor effects of apomorphine and a hypersensitivity to the stereotypy effects of apomorphine, while at 28 days post-hypophysectomy they are hypersensitive to both the locomotor and stereotypy effects of apomorphine. The hyposensitivity to the locomotor effects, at 7 days post-hypophysectomy, was associated with a decrease in ^{3}H-spiroperidol binding and an increase in tyrosine hydroxylase activity in the nucleus accumbens septi, whereas the hypersensitivity, at 28 days post-hypophysectomy, was associated with an increase in ^{3}H-spiroperidol and a decrease in tyrosine hydroxylase activity in the n. accumbens septi. The increased apomorphine-induced stereotypy in both the 7 and 28 days post-hypophysectomized animals was related to an increased ^{3}H-spiroperidol binding and a decreased tyrosine hydroxylase activity in the striatum. These behavioral and neurochemical data demonstrate that following hypophysectomy female rats will develop a transient decrease in dopamine receptor sensitivity in the n. accumbens septi, while the dopamine sensitivity in the striatum is increased. Thus the hypophysectomized female rat may prove to be a valuable model to study these two separate dopamine systems and their possible modulatory roles in the display of various behaviors.

Hypophysectomy Dopamine Spiroperidol Apomorphine Striatum Mesolimbic
Tyrosine hydroxylase Glutamic acid decarboxylase

CLASSICALLY the field of neuroendocrinology has studied the role of the brain and/or its neurotransmitters in modulating the hormonal output of the pituitary gland. The brain however, also functions as an endocrine organ as it is sensitive to the hormonal milieu of the organism. For example, hypophysectomy has been shown to result in an increase in ^{3}H-spiroperidol (^{3}H-spiro) binding in the striatum (STR; [19]). This effect on STR dopamine receptors can be demonstrated behaviorally as a hypersensitivity to the stereotypy effects of apomorphine (APO) and amphetamine [2,12]. A retrospective analysis of the dose-response curves for APO induced stereotypy from previous studies [19] indicated that the hypophysectomized (HYPOX) female rat was hyposensitive to the locomotor effects of APO. Since the locomotor effects of APO are thought to be mediated by the mesolimbic dopamine neurons (i.e., n. accumbens septi; ACB), this decreased locomotor response to APO may reflect a differential effect of HYPOX on the dopamine receptors in the STR and ACB. The present series of experiments were thus designed to study the effects of hypophysectomy on the potency of APO for inducing stereotypy behavior and locomotor activity. The tyrosine hydroxylase activity and ^{3}H-spiroperidol binding parameters were also determined in the STR and the ACB to assess the neurochemical changes associated with the altered APO potency of these dopamine rich areas of the forebrain. Moreover the glutamic acid decarboxylase (GAD) activity in the substantia nigra (SN) and ventral tegmental area (VTA) were also determined to assess possible neurochemical changes in the area of the dopamine cell bodies.

METHOD

HYPOX and sham HYPOX female Sprague-Dawley rats (180–200 g) were purchased from Hormone Assay Labs, Chicago, IL. All animals were ovariectomized (OVX) 2 days prior to the HYPOX or sham operation. HYPOX animals were maintained throughout the course of the experiment on normal saline. Animals were housed in group cages (5/cage) in a 12:12 light/dark cycle (lights on at 6:00 a.m.) with free access to food and water. Animals were sacrificed between 10 a.m. and 12 p.m. by decapitation and the brains were removed and placed on solid CO_2. Following sacrifice each animal was examined for completeness of HYPOX, and both the brain and behavioral data for that animal were discarded if the hypophysectomy was incomplete, or if there was obvious hypothalamic damage resulting from the surgery. Individual frozen brains were wrapped in aluminum foil and stored frozen at −80°C until dissection [14] and assay.

Dose-response curves for APO induced stereotypy and locomotor activity were determined on days 7, 14, 21, and 28 post-HYPOX. Each dose-response curve consisted of 7 doses (0.2, 0.4, 0.6, 0.8, 1.0, 1.5, and 2.0 mg/kg) of APO, with 5–7 animals/dose. The same group of HYPOX or sham

TABLE 1

ED50 VALUES FOR APOMORPHINE-INDUCED STEREOTYPY BEHAVIOR AND LOCOMOTOR ACTIVITY FOLLOWING HYPOPHYSECTOMY

	Days Post-Hypophysectomy			
	7	14	21	28
Stereotypy				
Sham	0.74	0.71	0.71	0.72
	(0.55–0.94)	(0.53–0.95)	(0.41–1.23)	(0.49–1.06)
Hypox	0.41*	0.36*	0.32*	0.36*
	(0.25–0.67)	(0.22–0.52)	(0.18–0.56)	(0.19–0.36)
Locomotor				
Sham	0.32	0.36	0.33	0.35
	(0.23–0.45)	(0.28–0.46)	(0.23–0.47)	(0.26–0.47)
Hypox	0.51*	0.36	0.28	0.16*
	(0.43–0.60)	(0.26–0.50)	(0.22–0.36)	(0.10–0.26)

Each value represents the estimated ED50 for apomorphine in mg/kg, over the (95% C.I.). The ED50 values were estimated by least squares linear regression analysis of the transformed data (i.e., probit vs. ln dose) and solving for the apomorphine value at y=5.0 (50% response). The 95% C.I. for each ED50 value was calculated by the methods described by Finney [10]. The ED50's for the sham and hypox group on each day were compared by a modified *t*-test as described by Finney [10].

*Denotes significant difference from sham group tested on the same day, *p* values of less than 0.05.

animals were used for all four dose-response curves. Animals were injected, IP, and placed in a wire mesh observation cage (15×30 cm, 20 cm high) and the resulting locomotor activity and stereotypy behavior scored during the 10–20 min post-injection period. Individual animals were observed for 30-second intervals every two min during the testing period and their locomotor activity and stereotypy behavior scored according to the following scales: Locomotor activity, 0=no locomotor activity (i.e., still), 1=grooming, 2=locomotion (all four legs moving), 3=rearing and/or climbing; stereotypy behavior, 0=no stereotyped behavior, 1=discontinuous "stereotyped" sniffing (intense sniffing directed towards either the sides or floor of the observation cage), 2=continuous "stereotyped" sniffing, 3=discontinuous licking and/or gnawing, 4=continuous licking and/or gnawing. The mean of all locomotor and all stereotypy scores observed during the testing period for each individual animal were then recorded as the behavioral scores for that animal. The animals (HYPOX or sham) were identified by ear markings following the behavioral test. The group mean for each dose of APO was then calculated and transformed into probits for the determination of the ED50 value using the methods described by Finney [10]. The ED50 values for the sham and HYPOX groups were then compared using a modified *t*-test [10].

The incidence of individual categories of behaviors following APO on days 7 and 28 post-HYPOX were also determined on a second set of HYPOX and sham animals. During this behavioral test animals were injected IP and observed for 10 separate 10 second intervals, during the 10–20 min post-injection period. The presence of specific categories of behavior were then recorded for each observation interval, similar to the methods described by Fray *et al.* [11]. The following behaviors were scored as present during the observation period, if the duration exceeded 3 seconds: (1) rearing and/or climbing; (2) stereotyped sniffing; (3) gnawing. The group incidence for the occurrence of individual behaviors were compared using the information statistic described by Robbins [21].

All biochemical assays were performed on the second set of HYPOX and sham operated animals. Animals were sacrificed on either day 8 or 29 post-HYPOX, 24 hours after the behavioral test. Additional HYPOX and sham animals, that were not tested behaviorally, were also sacrificed on these days to check for possible effects of the behavioral testing and/or APO treatment on the neurochemical endpoints. Moreover, the additional animals were required because several brains (n=10) were pooled to determine the ^{3}H-spiro binding parameters for the ACB.

The GAD activity in the SN and VTA were determined as described by Gordon *et al.* [13]. Tyrosine hydroxylase (TH) activity of the STR and ACB was assayed as described by Gordon *et al.* [14], using a substrate concentration of 5 μM.

The ^{3}H-spiro binding assays were performed according to the procedures described by Fields *et al.* [9], with slight modifications [19]. Low concentrations of ^{3}H-spiro (5–100 pM) were used to selectively label the high affinity site [18]. Individual animals were used to determine the K_D and B_{max} for ^{3}H-spiro binding in the STR, whereas pooled ACB (n=10) were required for the determination of K_D and B_{max} in the ACB. The amount of tissue per assay tube was held constant at 1.5 mg/tube for the STR and 3.0 mg/tube for the ACB. Tissue samples were homogenized in 100 volumes of 100 mM phosphate buffer (81 mM Na_2HPO_4, 19 mM KH_2PO_4) using a Brinkman polytron. The homogenate was centrifuged at 40,000 × g for 15 min and the supernatant discarded. The pellet was washed twice by resuspending in 100 volumes of buffer and centrifuging. The final pellet was resuspended in 100 volumes of phosphate buffer and aliquots (150 μl for STR and 300 μl for ACB) were added to the incuba-

tion tubes, resulting in a final volume of 2.2 ml. The assay tubes were then incubated at 37°C for 45 min in the presence or absence of (+)-butaclamol (10^{-6} M). The incubation was terminated by rapid filtration through Whatman GF/B glass fiber filters under vacuum, followed by two rapid (4.0 ml) rinses with ice-cold phosphate buffer. The total ^{3}H-spiro bound was then determined by liquid scintillation spectrometry. Specific ^{3}H-spiro binding was defined as the difference between the total binding in the absence and presence of (+)-butaclamol. Under these assay conditions 60–80% of the total counts bound to the filter were defined as specific binding. The Scatchard transformation of the data was analyzed by the method of least squares, linear regression analysis. The values for B_{max} and K_D reported in this paper are the mean of 6 individual animals for the STR or 6 pools of tissue for the ACB. All neurochemical results were analyzed by analysis of variance and Duncan's test [17].

RESULTS

At seven days post-HYPOX the dose-response data (Table 1) confirmed our previous report of a HYPOX-induced increase in APO potency for the induction of stereotypy behavior [19]. Moreover the HYPOX-induced hypersensitivity appeared to be relatively stable as the ED50 values for the induction of stereotypy in both the HYPOX and sham animals remained within the limits of the seven day value throughout the 4 weeks of testing (Table 1). Conversely, the HYPOX animals displayed a hyposensitivity to the locomotor effects on APO on day 7 post-HYPOX as indicated by the increased ED50 value. However, this hyposensitivity was transient as the HYPOX animals displayed a steady increase in APO sensitivity (i.e., decreasing ED50 values) to the locomotor effects of APO over the 4 weeks of testing. This steady increase in APO sensitivity resulted in the development of a hypersensitivity to the locomotor effects by 28 days post-HYPOX.

The incidence of individual categories of behavior (Fig. 1) were also indicative of a HYPOX-induced separation of the locomotor activity and the stereotypy behavior induced by APO (Fig. 1). The incidence of rearing and/or climbing in the 7 day post-HYPOX animals was decreased while the incidence of gnawing was increased, relative to the sham animals. By 28 days post-HYPOX the incidence of locomotor activity and gnawing were both increased. The incidence of stereotyped sniffing was apparently altered by the incidence of gnawing, in other words as the incidence of gnawing increased the incidence of sniffing decreased. Because of this apparent interaction of the HYPOX animals displayed a dose related decrease in the incidence of sniffing, while the sham HYPOX animals responded with a bell-shaped dose-response curve for the incidence of sniffing (Fig. 1).

The results of the ^{3}H-spiro binding assays were also indicative of a HYPOX-induced STR dopamine hypersensitivity, as both the 8 and 29 day post-HYPOX animals displayed an increase in B_{max} for ^{3}H-spiro binding to STR membranes (Table 2). The B_{max} for ^{3}H-spiro to ACB membranes appears to reflect the sensitivity of the HYPOX animals to the locomotor effects of APO (Table 2), as the B_{max} for ^{3}H-spiro was decreased in the 8 day post-HYPOX animals and increased in the 29 day post-HYPOX animals. No significant changes in the affinity (K_D) for ^{3}H-spiro were noted for any of the experimental groups or areas assayed in this study.

The TH activity in both the STR and ACB was inversely related to both the potency of APO and to the B_{max} for ^{3}H-spiro binding. The STR hypersensitivity to dopamine appeared to result in a compensatory decrease in the TH activity on both day 8 and 29 post-HYPOX (Table 2). The TH activity in the ACB also appeared to compensate for the postsynaptic sensitivity as it increased when the HYPOX animals were hyposensitive to the locomotor effects of APO, and decreased during the hypersensitivity to dopamine. The GAD activity was decreased in both the SN and VTR in both the 8 and 29 day post-HYPOX animals (Table 3).

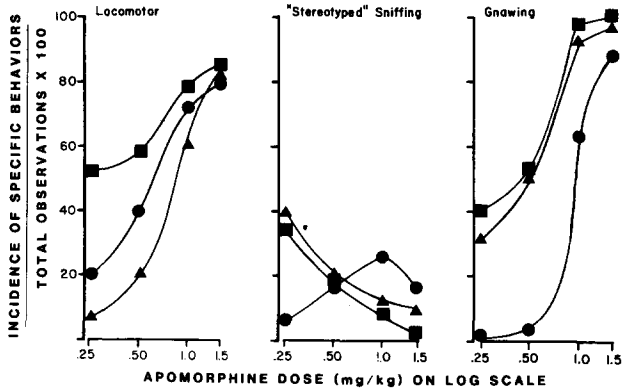

FIG. 1. The incidence of specific behaviors in hypophysectomized and sham-hypophysectomized female rats following apomorphine. All animals were ovariectomized 2 days prior to hypophysectomy or sham-hypophysectomy. Each point represents the percentage of total observations (i.e., proportion of observations) for 5 rats at each dose of apomorphine. Circles=sham-operated controls, triangles=hypophysectomized animals tested 7 days post-hypophysectomy, squares=hypophysectomized animals tested 28 days post-hypophysectomy. Information statistic [21] indicated significant differences in the locomotor and gnawing data matrices. The submatrices for these two behaviors indicated a significant treatment (i.e., HYPOX) effect on both behavioral responses. Partitioning of the submatrix for each of these behaviors indicated that both the 7 and 28 day post-HYPOX animals were significantly different from sham animals. Thus locomotor responses to apomorphine were reduced in the 7 day post-HYPOX group and increased in the 28 day post-HYPOX group, while both the 7 and 28 day post-HYPOX groups were significantly more responsive to the gnawing effects of apomorphine.

DISCUSSION

The present study confirms the ability of the pituitary to modulate central dopaminergic function [1, 2, 8, 12, 19]. Moreover, the results of this study suggest that HYPOX can produce the opposite effects on the dopamine sensitivity of the STR and ACB in the female rat.

Stereotypy behavior has been used extensively to assess the sensitivity of the nigro-striatal dopamine system. Normally, rating scales are used to evaluate the intensity of the stereotypy behavior [2, 4, 5, 12], and it has generally been assumed that increasing the dose of a dopamine agonist would result in a continuum of behaviors, although recent reports have cast doubt on this assumption [16,22]. Moreover, it has become apparent that not only will the type and dose of a dopamine agonist influence the behavioral results [11], but that the route of administration and the testing conditions [16] can also modify the results of the behavioral testing.

There is increasing evidence that stereotypy behavior can be divided into several components that may depend upon

TABLE 2

NEUROCHEMICAL ALTERATIONS IN THE STRIATUM AND N. ACCUMBENS SEPTI OF HYPOPHYSECTOMIZED FEMALE RATS

	^{3}H-Spiroperidol Binding			Tyrosine Hydroxylase	
	K_d (pmol)	B_{max} (fmol/mg tissue)	% Change in B_{max}	Activity (pmol/mg-hr)	% Change in activity
Striatum					
Sham	27.5 ± 3.9	13.9 ± 1.2	—	5.9 ± 0.2	—
Hypox (8)	40.4 ± 8.1	18.9 ± 2.4*	+36%	4.5 ± 0.3*	−24%
Hypox (29)	31.3 ± 3.1	20.8 ± 0.7*	+50%	5.1 ± 0.3*	−14%
Accumbens					
Sham	20.7 ± 4.5	4.0 ± 0.2	—	2.2 ± 0.2	—
Hypox (8)	21.9 ± 3.6	2.9 ± 0.1*	−28%	3.5 ± 0.5*	+59%
Hypox (29)	21.3 ± 4.2	4.8 ± 0.3*	+20%	1.7 ± 0.1*	−23%

All values represent the mean and s.e. of 6–8 individual animals or the mean of six assays on tissues pooled from ten animals (e.g. binding assays in the accumbens). The B_{max} and tyrosine hydroxylase activity are expressed per mg tissue.

Sham=sham operated controls; Hypox (8)=8 days post-hypophysectomy; Hypox (29)=29 days post-hypophysectomy; *=significant difference from sham value, analysis of variance and Duncans test.

separate underlying dopaminergic mechanisms and/or systems. Gnawing appears to be associated with stimulation of the basal ganglia [6,7], while the limbic areas are probably involved in the locomotor responses to dopamine agonists [15,23]. The data reported in this paper support the hypothesis that the mesolimbic dopamine system (i.e., ACB) may subserve a locomotor function as the decrease in APO-induced locomotor activity was associated with a decrease in the B_{max} for ^{3}H-spiro in the ACB. While the increased APO-induced locomotor activity was associated with an increased B_{max} for ^{3}H-spiro in the ACB. In contrast to the locomotor data, both the 7 and 28 day post-HYPOX animals were hypersensitive to the stereotypy effects of APO and both displayed an increased B_{max} for ^{3}H-spiro in the STR.

The TH activity was inversely related to the level of postsynaptic sensitivity, as indicated by the B_{max} for ^{3}H-spiro and the APO potency, in both the STR and ACB. In other words, the TH activity appears to compensate for, or is adjusted to, the level of postsynaptic sensitivity, thus when the postsynaptic sensitivity is increased the TH activity is decreased. This inverse relationship is particularly apparent in the ACB where both hypo- and hypersensitivity to dopamine are seen in the HYPOX animals (Table 2).

In non-HYPOX animals the GAD activity appears to adjust to (or compensates for) the level of postsynaptic dopamine sensitivity in the STR, as the GAD activity in the non-HYPOX animals changes in a direction that would be predicted by the proposed inhibitory influence of GABA on the firing rate of dopamine neurons in the SN [3, 13, 14]. However, this is not the case in the HYPOX animals as they show a decreased GAD activity which in the non-HYPOX animals would be indicative of a decreased postsynaptic sensitivity, and an increase synthesis capacity [13, 14, 19]. Thus the GAD activity in the SN and VTA of the HYPOX animals appears to be unrelated to both the postsynaptic sensitivity and the TH activity in the STR and ACB. These data would seem to indicate that the HYPOX animals either have an altered GABA neuronal feedback or that the gabaergic output from the SN/VTA is altered [24]. Alternatively, some other regulatory mechanism may have superceded the neuronal feedback system to decrease the TH activity in the HYPOX animals [3].

TABLE 3

HYPOPHYSECTOMY INDUCED CHANGES IN GLUTAMIC ACID DECARBOXYLASE ACTIVITY

	SHAM	HYPOX (8)	HYPOX (29)
Substantia nigra	12.8 ± 0.7	9.8 ± 0.6*	10.9 ± 0.2*
Ventral tegmentum	8.3 ± 0.7	6.0 ± 0.3*	6.8 ± 0.6*

Values represent the mean and S.E. of 6 individual animals.
Units=nmole/mg tissue-hour.
SHAM=sham operated control.
HYPOX (8)=8 days post-hypophysectomy.
HYPOX (29)=29 days post-hypophysectomy.
*=Significant difference from control animals. Analysis of variance and Duncan test ($p<0.05$).

The results reported in this paper do indicate that the integrity and/or function of the brain dopamine systems, in the rat, may be dependent upon or modulated by a pituitary secretion(s). Moreover, these data indicate that the HYPOX female rat will develop a transient decrease in ACB dopamine sensitivity at a time when STR dopamine sensitivity is increased. Very few non-invasive experimental manipulations will differentially effect the mesolimbic and nigro-striatal dopamine sensitivity, thus the HYPOX female rat may be a valuable model to study these two separate dopamine systems and dissect their functional role in modulating various behaviors.

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