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Journal
Life Sciences, 39(19)

ISSN
0024-3205

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Publication Date
1986-11-01

DOI
10.1016/0024-3205(86)90095-0

Life Sciences, Vol. 39, pp. 1755-1763 Pergamon Journals
Printed in the U.S.A.

PERSISTING SUBSENSITIVITY OF THE STRIATAL DOPAMINE SYSTEM AFTER FETAL EXPOSURE TO β-ENDORPHIN

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(Received in final form August 8, 1986)

Summary

Fetal exposure of rats to β-endorphin during the third trimester, either alone or with α-MSH, resulted in mild developmental delay and significant decreases in striatal dopamine receptor density (subsensitivity) persisting through maturity. The apparent paradoxical down-regulation of dopamine receptors in the presence of β-endorphin was consistent with fetal exposure to dopamine receptor antagonists and synthesis inhibitors. These findings suggest biophysical properties of receptors which are unique to fetal development including loss of plasticity after exposure to antagonists. Permanent, down-regulation of the striatal dopamine system may be one mechanism underlying delayed development after fetal exposure to β-endorphin which may accompany hypoxia. Even though there were no statistically significant differences between males and females in density of the dopamine receptor, the behavioral profile after peptide treatment was sexually demorphic. Behaviorally, female rats appeared sensitized to perinatal α-MSH and males to α-endorphin.

Elevated β-endorphin (an endogenous opiate peptide) in amniotic fluid is associated with prenatal hypoxia and acidosis (1-4), the most common antecedents of perinatal central nervous system damage (5). Prenatal exposure of rats to high levels of β-endorphin retards development and interferes with learning and memory (6), without apparent changes in brain β-endorphin immunoreactivity (7). Pretreatment of pregnant rabbits with the opiate antagonist naloxone, blocking the influence of β-endorphin, protects the fetus from the effects of experimentally induced maternal hypoxia (8), further implicating endogenous opiates in prenatal development.

Although located in the same preprotein molecule (pro-opiomelanocortin) as β-endorphin (9), α-MSH has growth promoting properties in utero (10). During fetal development α-MSH is the primary tropic hormone for the adrenals (11), stimulates secretion of the sebaceous vernix (12) and is present in the brain during early stages and then declines (13). When administered to neonatal rats, α-MSH can induce an enduring enhancement of learning and memory (14, 15), but

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0024-3205/86 $3.00 + .00

the effects of prenatal exposure are unknown.

Many of the central nervous system effects of these peptides in the adult are mediated by dopamine (DA) (16). Even though opiates and DA agonists do not bind to each other's receptors (except at high doses) both pre- and post-synaptic mechanisms have been implicated in their reciprocity (17). DA antagonists have many of the same effects as morphine (18-20) suggesting presynaptic inhibition of DA release, related to co-location of opiate receptors on DA terminals (21- 24). Inhibition of DA release by β-endorphin in the presence of K+ (25-27) and its disinhibition by naloxone (25) is further support for this possibility. In contrast, α-MSH stimulates dopamine release (28, 29). These related peptides may exert reciprocal effects which influence nervous system development. We now report that prenatal exposure of rats to high levels of β-endorphin during the third trimester, with or without co-adminstration of α-MSH, decreases dopamine receptor density in the striatum which persists into adulthood.

Materials and Methods

Multiparous pregnant rats (Sprague-Dawley) were injected s.c. on days 14-21 of pregnancy (third trimester) with β-endorphin (100 ug/rat), α-MSH (100 ug/rat), α-MSH + β-endorphin (100 ug/rat) or a vehicle solution (0.5 ml, 0.01 M acetic acid in 0.9% NaCl). The male (N=51) and female (N=42) pups were observed from birth through adulthood. Since previous studies (6) indicated that maternal behavior was not responsible for changes observed in the offspring (i.e., effect of cross-fostering), all animals were reared by their biological mother. Several behavioral tests were administered and striatal dopamine receptors were studied by H-Spiperone binding to striatal membranes.

Animals were observed daily for eye opening and were weighed on days 4, 19, and 69. Previous reports indicated that the startle response of adult rats to acoustic stimuli, an index of "reflexive" attention (30, 31), was attenuated in rats exposed to β-endorphin during the 2nd and 3rd trimester of fetal life (6), and in adulthood (32). Thus, on day 75, rats were tested in an enclosed cylinder containing a ballistiographic platform to record the motor startle reflex. Thirty-three acoustic stimuli (118 dB, 60 msec 1000 Hz square wave tone) were delivered through speakers in a sound dampened chamber. The first 3 stimuli were delivered at a rate of one per minute (these were used for calibrating the startle apparatus). The remaining 30 were delivered at a rate of four per minute. Ten of the last 20 acoustic stimuli were preceeded (150 msec) by a flash of light.

Since earlier studies indicated that neonatal exposure of rats to β-endorphin chronically altered pain threshold (33), assessment of pain threshold was done on day 90 with the tail flick test (34). Prenatal treatment sensitizes rats to morphine (6), thus one group of animals was challenged with a dose of morphine (2mg/kg) on day 110. Since treatment with morphine may alter the neurochemistry, a separate group of rats was sacrificed by decapitation for study of dopamine receptors.

The brains were placed on ice, the striata dissected rapidly and homogenized in 30 volumes of ice-cold buffer (50 mH Tris-HCl, pH 7.7 at 25°C) in a Brinkman Polytron homogenizer (setting 6 for 20 sec.). The homogenate was centrifuged at 48,000 g for 20 min in a refirgerated centrifuge and the pellet resuspended in fresh buffer and recentrifuged at the same rate and the same time. The final pellet was suspended in 50 mM Tris buffer (pH 7.4 at 25% C con-

taining 120 mM NaCl, 5 mM KCl, 2 mM CaCl and 0.% of ascorbic acid) yielding 10 mg wet tissue per ml buffer.

For the binding assay 0.2 ml of the homogenate, containing approximately 0.2 mg protein, were incubated with 0.2 ml of 20-200 pM concentrations of $_3$H-Spiperone (s.p. activity 23.05 Ci/mmole, NEN) and 0.2 ml of 3 uM + or - butaclamol (Ayrest). Incubations were carried out in triplicate at 37° C for 15 min. At the end of the incubation the contents of the incubation tubes were diluted with 5 ml ice-cold 50 mM Tris buffer (pH 7.4 at 25°C) and rapidly filtered under partial vacuum using a Millipore manifold filtration unit and Whatman FG/B fiber filters. The filters were washed with two 5 ml of the same buffer, dried and transferred to liquid scintillation vials. Radioactivity was counted after overnight equilibration in 20 ml scintillation fluid. Protein was determined by the method of Lowry, Rosenbough, Farr and Randall (35).

Several studies indicate two spiperone binding sites in brain, including the corpus striatum (36-38). A nondopaminergic, probably serotoninergic, component is implied for lower affinity binding sites when high ligand concentrations are used (39,40). High affinity binding sites (with dissociation constants in the range of 24 - 170 pM) at low ligand concentrations, have a relatively high specificity for dopamine (36-38). In this study low ligand concentrations were used to study the binding sites that are considered specific for dopamine. Specific binding was defined as the difference between binding in the presence of (-) butoaclamol and (+) butoaclamol. The dissociation constants (Kd) and the maximal binding capacity (Bmax) for $_3$H-spiperone were calculated from Scatchard plots generated by the least square regression analysis.

Results

Density of dopamine receptors were decreased in offspring of mothers exposed to high levels of β-endorphin. Analysis of Scatchard plots (Figure 1)

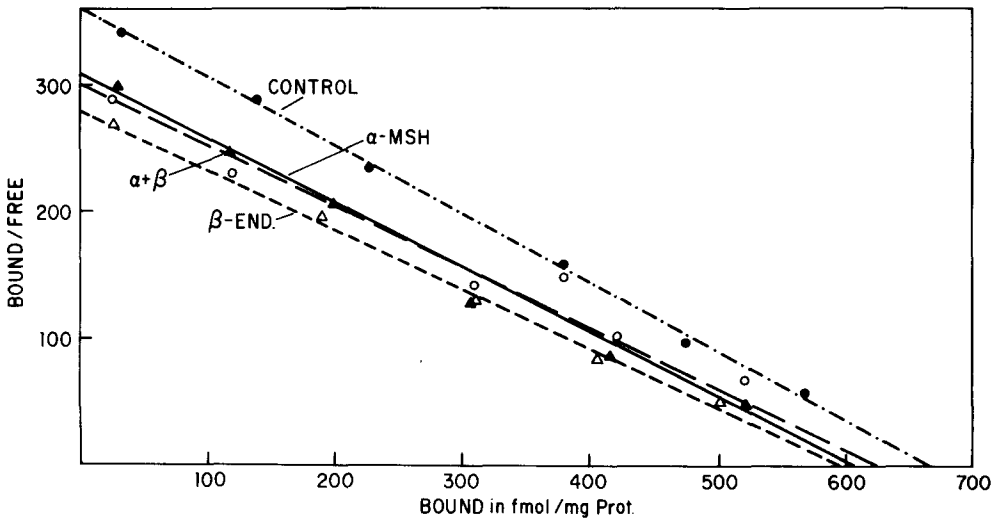

FIG. 1

Scatchard plots illustrating decreased density of dopamine receptors in adult rats after treatment in utero, with β-endorphin, α-MSH, β-endorphin + α-MSH or the vehicle solution.

showed that the changes were due to a reduction of receptor density (Bmax) rather than affinity (Kd). None of the effects of early exposure to α-MSH were statistically significant (Table I).

TABLE I

$^{3}_{H}$-Spiperone Binding to Striatal Membranes of Rats Following Intrauterine Treatment with α-MSH and β-endorphin (Expressed as Percentage Change).

	K_D (pM)			B max (f moles/mg protein)		
	Combined	Males	Females	Combined	Males	Females
Control	57 ± 8*	62 ± 7	52 ± 9	100 ± 6	100	92
α-MSH	63 ± 4	65 ± 4	71 ± 5	90 ± 7	90	104
β-Endorphin	61 ± 4	52 ± 1	70 ± 7	80 ± 6**	80*	84
β-MSH + Endorphin	50 ± 7	52 ± 9	48 ± 6	76 ± 8**	76*	74*

* Values are means ± S.E.M. of eight animals run in triplicates.
** $p < 0.05$ Student's T-test.

As presented in Table I, combined treatment with α-MSH and β-endorphin had identical influences on males and females. Early exposure to α-MSH increased dopamine receptor only in the females (although, not statistically significant). Perinatal exposure to β-endorphin decreased dopamine receptor density in both sexes, however, only in the males was the downregulation statistically significant. The co-administration of α-MSH was ineffective in balancing the influence of early exposure to β-endorphin in both sexes. Thus, the presence of high levels of β-endorphin in pregnant rats appears sufficent for enduring, down-regulation of the dopamine system in offspring.

The analysis of behavioral effects was computed with the influence of litters evaluated as suggested by Abbey and Howard (41) and Chapman and Stern (42). If the effect of litter was significant, its mean square error term and degrees of freedom were used as the denominator to test for the experimental effect. If the effect of litter failed to reach significance, it was combined with the error term as the denominator. Thus, a very conservative analysis of experimental effect on behavior was employed. Virtually all of the effects of peptides were statistically significant with conventional analyses (i.e., when the influence of litter was ignored).

Table II presents the results of prenatal peptide exposure on behavioral variables. There were no consistent differences in litter size for the groups. Of the 7 deaths, 5 were from the β-endorphin group ($p < .06$ by binomial expansion). As in previous reports (6, 43), there was a trend suggesting that α-MSH accelerated, and β-endorphin delayed eye-opening, however, the influence of

litter membership compromised the main effect of treatment. Rats exposed to α-MSH in utero were heavier at day 4 ($F(1,4) = 9.51$, $p < .05$). This trend was evident at day 19 but not by day 69. For the female but not the male rats, early exposure to α-MSH exacerbated both the habituated ($F(1,4) = 7.43$, $p < .06$) and nonhabituated ($F(1,4) = 8.51$, $p < .05$) startle response (Table II). The effect with male rats was not significant.

TABLE II

Behavioral Profiles of Rats Treated In Utero with β-endorphin and α-MSH (Males = 51; Females = 42)

Variables	In Utero Treatments			
			β-endorphin +	
	β-endorphin	α-MSH	α-MSH	Vehicle
Number	25	20	23	25
males	13	11	11	16
females	12	9	12	9
Deaths	5	0	0	2
Weight (gross)				
Day 4	10.8	11.8*	11.1	10.4
19	37.9	42.4	38.8	35.5
69	265	281	279	240
Day of Eye Opening	13.5	12.5	12.8	13.2
Activity Count	45.3	44.2	42.3	42.5
Startle (counts)				
No Habituation				
(males)	113.9	39.8	99.2	47.1
(females)	45.6	120.5*	131.1*	49.2
Habituation				
(males)	48.9	22.6	56.0	33.9
(females)	32.3	73.3*	88.5*	41.8
Males Only (Seconds)				
Tail Flick (placebo)	4.5*	4.3	4.6*	3.8
(morphine)	6.1	7.4*	7.5*	6.8

* $p < 0.05$

Rats exposed to β-endorphin in utero evidenced significantly ($F(1,24) = 5.56$, $p < .05$) greater pain tolerance than rats treated with α-MSH or the vehicle. Exposure to α-MSH but not β-endorphin was synergistic with morphine administered in adulthood resulting in significantly ($F(1,24) = 8.91$, $p < .01$) longer latencies (i.e., higher pain threshold) than other treatment groups. Thus, exposure to β-endorphin during the third trimester elevated pain threshold

without influencing the response to morphine, implying minimal changes in the opiate receptor. Conversely, early exposure to α-MSH may result in supersensitivity of the opiate receptor.

Discussion

Persisting down-regulation of dopamine receptors after prenatal exposure to β-endorphin is consistent with studies of dopamine blockers and supports the suggestion that the mechanisms governing prenatal receptor sensitivity are different than in postnatal development. Administration of dopamine blockers to mature animals results in transient receptor supersensitivity (44). However, exposure of pregnant rats to dopamine receptor blockers (neuroleptics) or dopamine synthesis inhibitors (a-methyl-p-tyrosine) results in down-regulation of dopamine receptors in offspring persisting into maturity (45, 46). Conversely, prenatal exposure to L-dopa (increasing DA synthesis) increases receptors in offspring (47). The recent report (48) of permanent alterations in dopamine dependent sexual behavior after prenatal exposure to dopamine agonists and antagonists indicates that receptor and behavioral plasticity may be restricted by fetal experience. Neither the schedule nor mechanism for the development of dopamine receptor regulation is certain, however, it appears to occur in rats sometime between day 6-15 postnatally (45-46). Thus, the persisting down-regulation of dopamine receptors in rats exposed in utero to dopamine blockers may be confined to critical periods of brain organization. This may be especially significant for β-endorphin since it is elevated in amniotic fluid with hypoxia and may serve as a marker for fetal brain development.

For example, prenatal exposure to β-endorphin may be a critical factor in the central nervous system development. A 2-20 fold increase in amniotic fluid content of β-endorphin is associated with fetal hypoxia and acidosis (1-4). Although the deleterious effects of hypoxia are documented, its mechanism is not. Since neither specific changes in opiate receptors nor in β-endorphin content in the brains of rats exposed prenatally to high levels of β-endorphin have been reported (7), the role of β-endorphin has been unclear. Further, its passage of the placental barrier is uncertain (49-50), although the placenta has receptors for, and may synthesize and release β-endorphin (51-55). Fetal circulation is modulated by β-endorphin (56) but it is not known if amniotic content of β-endorphin is a fetal reflection, or a significant maternal cause, of reduced fetal oxygen. The present results suggest that β-endorphin may exert its influence on fetal development by influencing the DA system. The selective sensitivity of brain dopamine to altered oxygen (57-58) which also resulted in elevated β-endorphin is consistent with this possibility. Thus, decreased dopamine receptor density may be one mechanism related to developmental delay following fetal exposure to high levels of β-endorphin.

There were two interesting behavioral findings after maternal challenge with β-endorphin and α-MSH. First, although several effects were statistically significant, the magnitude and pattern was different than was observed in earlier studies when injections were made during the second and third trimester (6) or after neonatal treatment (33). Rats exposed in utero to β-endorphin during the second and third trimester displayed severe restriction in activity and startle responses and were sensitized to morphine challenge. Neonatal exposure to β-endorphin (33) resulted in "chronic" insensitivity to a thermal stimulus. In the present study a less robust effect, though significant, was observed. Clearly, these inferential and incomplete comparisons suggest that the timing and perhaps duration of exposure in utero, to β-endorphin are reflected in characteristic behavioral patterns. This possibility is entirely consistent

with the recent report of Zadina et al (59) who showed decreased μ opiate receptors in adult brain after prenatal β-endorphin treatment but increased receptor density when treatment was administered neonatally.

The second behavioral finding of interest was the sexually-dimorphic influence of prenatal peptide treatment. Early exposure of female rats to α-MSH resulted in exaggerated startle responses. The pattern in males was reversed. Furthermore, the effect of treatment with both α-MSH and β-endorphin on the startle response resembled the α-MSH-only treatment condition in females, but the β-endorphin-only treatment condition in males. With the methods used, the male rats appeared more susceptible to β-endorphin, whereas the females were more sensitive to α-MSH. This behavioral dimorphism was paralleled partially by the differential sensitivity of α-MSH and β-endorphin on the density of dopamine receptors. Although this pattern has not been reported before, sexually-dimorphic responses to perinatal influences has been observed in several experiments. For example, neonatal treatment with -MSH improved the visual discrimination of adult male but not female rats (15). In a separate experiment perinatal exposure to α-MSH increased the time in contact of female but not male rats in an open field (60). In a comprehensive study of a series of perinatal treatments of varying times after gestation, Grimm and Frieder (61) concluded that male rats suffered deleterious consequences of prenatal insults far more often than female rats.

The pattern of responses for males and females differed in the present study. Males appeared to be influenced more than females by prenatal exposure to β-endorphin. Females responded more than males to α-MSH. Since perinatal β-endorphin has growth-retarding properties (6), these results are consistent with those indicating that males are more susceptible than females to a variety of teratogenic agents (61). The behavioral differences between the males and females after in utero exposure to α-MSH and β-endorphin is especially interesting in view of effects on dopamine receptors. Even though there were similar changes in brain dopamine for males and females after treatment with α-MSH and β-endorphin, behavioral patterns were decidedly sexually dimorphic. It is possible that neurotransmitter - neuropeptide relationships are coupled to behavior in sexually-dependent ways.

Acknowledgement

Supported in part by a grant from John D. and Catherine T. MacArthur Foundation, Network on Risk and Protective Factors of Mental Illness.

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