ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol. Exp. 1998, 58: 221-225

Prenatal exposure to anticonvulsant drugs and spatial ability in adulthood

Arianne Dessens[1], Peggy Cohen-Kettenis[2], Gideon Mellenbergh[3], Nanne van de Poll[3], Janna Koppe[1] and Kees Boer[1]

[1]Academic Medical Center, University of Amsterdam, Department of Obstetrics, Gynecology and Neonatology, Graduate School Neurosciences Amsterdam, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands, Email: a.b.dessens@amc.uva.nl; [2]Rudolf Magnus Institute of Neurosciences, Department of Child and Adolescent Psychiatry; [3]University of Amsterdam, Faculty of Psychology

Short communication

Abstract. By disturbing steroid hormone balances in the fetus, the anticonvulsant drugs phenobarbital and phenytoin may affect certain aspects of cognitive functioning. In order to test this hypothesis, we studied hormone related cognitive functioning in 72 men and 75 women who had been prenatally exposed to these drugs and equal numbers of matched control subjects. The groups did not differ on word fluency, dichotic listening and a Water Level Test. On Card Rotations, however, anticonvulsant-exposed males and females obtained significantly lower scores than control subjects. These results suggest that in both males and females prenatal exposure to phenobarbital and phenytoin may affect holistic spatial processing.

Address for correspondence:
Arianne Dessens
Delta Psychiatric Hospital
P.O. Box 800
3170 DZ Poortugaal
The Netherlands

Key words: prenatal exposure-delayed effects, anticonvulsants, steroids, spatial processing

There is growing evidence that gonadal hormones are involved in brain development of the fetus and newborn. Anatomical as well as functional differences between male and female brains have been found in structures that are related to both reproductive and non-reproductive functioning (Collaer and Hines 1995). Animal research has shown that gonadal hormones play an important role in the development of neural tissue, and that pre- or perinatal manipulation of steroids, particularly testosterone, changes sex-specific behaviors (Collaer and Hines 1995, Panzica 1995). A couple of human studies have been performed on the relationship between prenatal circulating testosterone and certain aspects of cognitive functioning: these studies have been carried out in subjects who had been prenatally exposed to altered gonadal hormonal balances, caused by an idiopathic condition or by prenatal exposure to medication (Collaer and Hines 1995), and in non-clinical populations (Jacklin et al. 1988, Finegan et al. 1992, Grimshaw et al. 1995, Udry et al. 1995). Although the interactions between prenatal steroids and cognitions appeared to be complicated, in both men and women indications were found that a higher level of pre- or perinatal testosterone is related to enhanced visuospatial abilities, and perhaps also to diminished verbal abilities.

In male rodents early exposure to phenobarbital and phenytoin leads to demasculinization (Gupta et al. 1982, Reinisch and Sanders 1982). In females it disturbs reproductivity (Gupta 1980) and may enhance spatial processing (Fonseca et al. 1976, Mullenix et al. 1983).

Phenobarbital and phenytoin have been and continue to be frequently prescribed anticonvulsant drugs. They are usually continued during pregnancy. This study was carried out in order to investigate whether prenatal exposure to phenobarbital and phenytoin influence cognitive functioning of human adults. It was hypothesized that if prenatal exposure to these anticonvulsants metabolize steroids in the fetus, cognitive abilities such as verbal and spatial abilities and functional asymmetry in processing of verbal stimuli, would be less pronounced.

The study was carried out in subjects who have been prenatally exposed to phenobarbital and/or phenytoin with or without amphetamines and in control subjects matched for sex, age (born less than one week before or after an exposed child) and their mother's age (plus or minus two years). The subjects were born between January 1957 and December 1972 after at least 30 weeks of gestational age. Most mothers of the exposed subjects took medication because they had a seizure disorder, 22 mothers took phenobarbital because of nausea, insomnia or emotional problems. In addition to their anticonvulsant medication, 22 epileptic mothers received amphetamines to prevent anticonvulsant-induced drowsiness. By now, no teratogenic influences or long-term consequences of prenatal exposure to amphetamines, have been found (Briggs et al. 1994, Erikson and Zetterström 1994). The mothers did not have any other pre-existing pathology and did not receive additional medication. Mothers of the control subjects neither had any pre-existing pathology, nor did they take medication during pregnancy.

After their current addresses had been traced, the subjects received a letter in which they were informed about the study and were asked to participate. We contacted 243 prenatally exposed and 222 control subjects. Of them, 72 prenatally exposed males, 75 prenatally exposed females and equal numbers of control males and females volunteered (response rates respectively 61% and 66% among anticonvulsant-exposed and control subjects).

In order to test for cognitive functioning, instruments were selected that are known to measure the largest sex-differences (Linn and Petersen 1986, Hyde and Linn 1988): Card Rotations (Kit of Reference Tests for Cognitive Factors, Ekström 1976), the Water Level Test (Gladue 1990) and Word Fluency tests (Groninger Test for Intelligence, Snijders and Verhage 1983). A dichotic listening test was selected to measure functional asymmetry for auditory-verbal perception (Bouma 1984). Left and right handedness was assessed by a questionnaire (Van Strien 1988). In addition, the similarities subtest of the Wechsler Adult Intelligence Scales (WAIS) was used to have an estimate of the general level of intellectual functioning (Stinissen et al. 1970); this subtest has the highest correlation with total WAIS-score (Lezak 1983). Parental educational level and socio-economic status and the subjects education and socio-economic status were measured by means of a questionnaire. Socio-economic status was categorized according to a Dutch classification system (ITS 1991).

Differences between prenatally anticonvulsant-exposed and control groups were tested by analyses of variance (anova) for correlated measurements. In order to find differences between the medication groups, analyses were repeated in the phenobarbital monotherapy and phenobarbital plus phenytoin groups and their controls; in these analyses medication was taken as a factor. Since no differences were found between the various medication groups, only those results are presented in

which all drug-exposed groups are compared to the control group. Data on the socio-economic status and education were analyzed by means of Wilcoxon matched pairs rank sum tests. Results revealed that groups did not differ on socio-economic status, parental educational level or parental socio-economic status.

On Card Rotations anticonvulsant-exposed subjects obtained lower scores than control subjects (P=0.01). However, it was also found that more anticonvulsant-exposed subjects had attended specialized schools for children with learning problems (P=0.00). Further analyses demonstrated that these subjects with learning problems had significantly lower scores on most cognitive tests and tended to lower the scores of the entire anticonvulsant-exposed group (Dessens 1996). To check whether the significant differences between groups on Card Rotations was caused by differences in intelligence between groups, an additional analysis of covariance

TABLE I

Results on spatial and verbal processing and hemispheric asymmetry

	Group	Sex	n		Mean	SD	P-value	
Card Rotations								
	exposed	males	72		109	(21)		
	controls	males	72		112	(21)	sex:	0.000
	exposed	females	68		93	(23)	condition:	0.001
	controls	females	68		106	(25)	sex by condition:	0.07
Water Jars								
	exposed	males	70		76	(111)		
	controls	males	70		57	(104)	sex:	0.000
	exposed	females	72		162	(142)	condition:	0.13
	controls	females	72		134	(138)	sex by condition:	0.76
Word Fluency								
animals	exposed	males	71		25	(6)		
	contros	males	71		25	(6)	sex:	0.76
	exposed	females	75		25	(5)	condition:	0.97
	controls	females	75		25	(5)	sex by condition:	0.83
Professions	exposed	males	68		18	(6)		
	controls	males	68		20	(4)	sex:	0.15
	exposed	females	73		17	(4)	condition:	0.02
	controls	females	73		19	(5)	sex by condition:	0.63
Dichotic Listening								
right-handed subjects[1]	exposed	males	48	right ear	38.65	(7.5)		
				left ear	35.0	(8.7)	sex:	0.60
	controls	males	48	right ear	39.92	(6.8)	condition:	0.66
				left ear	36.0	(7.2)	ear:	0.00
	exposed	females	51	right ear	38.53	(7.2)	sex by condition:	0.38
				left ear	35.77	(7.3)	sex by ear:	0.39
	controls	females	51	right ear	38.18	(6.7)	condition by ear:	0.88
				left ear	35.35	(6.4)	sex by condition by ear:	0.94

[1] The dichotic listening test was not done in subjects with hearing problems. As only one left-handed female prenatally anticonvulsant-exposed and control pair remained for analysis, this analysis has not been carried out in left handed subjects.

with the subject's score of the WAIS similarities subtest as the covariate was performed. Despite a significant influence of the covariate, the differences between groups on Card Rotations remained significant. Anticonvulsant-exposed subjects also made more mistakes on the Water Level Test, but the difference between the groups was not significant (P=0.13). As expected, males outperformed females on the selected tests for mental rotation (P=0.00 for sex on both Card Rotations and Water Level Test). Contrary to expectation, no differences between groups or sex were found on the two trials of the word fluency test and the dichotic listening task. No interaction effects were found on the tests used in this study.

Results are summarized in Table I.

In this study it was found that subjects prenatally exposed to phenobarbital and phenytoin and their matched controls performed similarly in several cognitive functions that may be influenced by prenatal exposure to sex hormones. Spatial ability seemed to be slightly deteriorated by prenatal exposure; the effect was observed in both males and females. This last finding indicates that, in general, anticonvulsant-exposed subjects had more difficulties in mental rotation than control subjects. The fact that no significant effect was found for the Water Level Test may be due to differences between the two tests in their demand for abstract and concrete thinking, which, in the case of the Water Level Test, makes it easier to rely on verbal strategies or learning experiences. These stategies are probably not useful in the case of the Card Rotations. It is assumed that Card Rotations is more heavily dependent on holistic visuospatial processing, a cognitive action in which the right temporo-parietal lobe is strongly involved (Lezak 1983).

Research in animals on effects of early hormonal actions on brain development showed that, in male rats, androgens suppress left cortex growth (Steward and Kolb 1994) so that the right cortex becomes thicker than the left (Diamond et al. 1981). Androgen deficiency may prevent this organizing influence which may lead to a disadvantage in spatial ability that will never disappear. It is unknown whether this theory, which is based on findings in animals, also applies to human brain development. The results in our study suggest that prenatal changes in steroid balances had some influence on cognitive functioning in humans, but the effect in humans seems to be different from that in animals, as impaired mental rotation ability was not only observed in men but also in women. Geschwind and Galaburda (1985) have proposed that androgens increase the functional potency of the right hemisphere, but the precise mechanism by which these steroids affect the lobe is still unknown.

This study was supported by a grant of the Netherlands Fund for Research in Mental Health (Nationaal Fonds voor de Geestelijke Volksgezondheid) no. 3393.

Bouma A., van Strien J. W., Bekker C., Tjerkstra A. (1984) Dichotic listening and tactual mental rotation in females as a function of familial sinistrality and strength of handedness. J. Clin. Neuropsychol, 6: 171-188.

Briggs G. G., Freeman R. K., Yaffe S. J. (1994) Drugs in pregnancy and lactation. A reference guide to fetal and neonatal risk. (Fourth ed.). Williams and Wilkins, Baltimore, USA, p. 44a-51a.

Collaer M. L., Hines M. (1995) Human behavioral sex differences: a role for gonadal hormones during early development. Psychol. Bull. 118: 55-107.

Dessens A. B. (1996) Prenatal exposure to phenobarbital and phenytoin. A study on long-lasting consequences. Thesis, Medical Faculty, University of Amsterdam.

Diamond M. C., Dowling G. A., Johnson R. E. (1981) Morphological cerebral cortical asymmetry in male and female rats. Exp. Neurol. 71: 261-268.

Ekström R. B., French J. W. Harman H. H. Durmen D. (1976) Kit of factor-reference cognitivetests. Educational testing service Princeton, NJ.

Eriksson M., Zetterström R. (1994) Amphetamine addiction during pregnancy: 10 year follow-up. Acta Paediatr. (Suppl). 404:27-31.

Finegan J. A. K., Niccols G. A., Sitarenios G. (1992) Relations between prenatal testosterone levels and cognitive abilities at 4 years. Dev. Psychol. 28: 1075-1089.

Fonseca N. M., Sell A. B., Carlini E. A. (1976) Differential behavioral responses of male and female rats treated with five psychotropic drugs in the neonatal stage. Psychopharmacologia 46: 263-268.

Geschwind N., Galaburda A. M. (1985) Cerebral lateralization. Biological mechanisms, associations and pathology: I. A hypotheses and a program for research. Arch. Neurol. 42: 428-459.

Gladue B. A., Beatty W. W., Larson J., Staton R. D. (1990) Sexual orientation and spatial abilty in men and women. Psychobiology 18: 101-108.

Grimshaw G. M., Bryden M. P., Finegan J. A. K. (1995) Relations between prenatal testosterone and cerebral lateralization in children. Neuropsychology 9: 68-70.

Gupta C., Sonawane B. R., Yaffe S. J. (1980) Phenobarbital exposure in utero: alterations in female reproductive function in rats. Science 208: 508-510.

Gupta C., Yaffe S. J., Shapiro B. H. (1982) Prenatal exposure to phenobarbital permanently decreases testosterone and causes reproductive dysfunction. Science 216: 640-641.

Hyde J. S., Linn M. C. (1988) Gender differences in verbal ability: a meta-analysis. Psychol. Bull. 104: 53-69.

ITS - A Dutch classifications of professions. (1991) Institute for applied social sciences. (ITS Beroepenklapper. Instituut voor toegepaste sociale wetenschappen). Nijmegen, The Netherlands.

Jacklin C. N., Wilcox K. T., Maccoby E. E. (1988) Neonatal sex-steroid hormones and cognitive abilities at six years. Dev. Psychobiol. 21: 567-574.

Lezak M. D. (1983) Neuropsychological assessment. Oxford University Press Inc, Oxford, p. 265-266.

Linn M. C., Petersen A. C. (1986) A meta-analysis of gender differences in spatial ability: implications for mathematics and science achievement. In: The psychology of gender (Eds. J. S. Hyde and M. C. Linn). John Hopkins University Press, Baltimore, p. 67-99.

Mullenix P,. Tassinari M. S., Keith D. A. (1983) Behavioral outcome after prenatal exposure to phenytoin in rats. Teratology 27: 149-157.

Panzica G. C., Aste N., Viglietti-Panzica C., Ottinger M. A. (1995) Structural sex differences in the brain: influence of gonadal steroids and behavioral correlates. J. Endocrinol. Invest. 18:232-252.

Reinisch J. M., Sanders, S. (1982) Early barbiturate exposure: the brain, sexually dimorphic behavior and learning. Neurosc. Biobehav. Rev. 6: 311-319.

Snijders J. Th., Verhage F. (1983) Groninger test for intelligence (Groninger Intelligentie Test). Swets and Zeitlinger B.V. Lisse, The Netherlands.

Steward J., Kolb, B. (1994) Dendritic branching in cortical pyramidal cells in response to ovariectomy in adult female rats: suppression by neonatal exposure to testosterone. Brain Res. 654:149-154.

Stinissen J., Willems P. J., Coetsier P. Hulsman W. L. L. (1970) Guide to the Dutch adaptation of the W.A.I.S. (Handleiding bij de Nederlands bewerking van de Wechlser Adult Intelligence Scale - W.A.I.S.) Swets and Zeitlinger B.V. Lisse, The Netherlands.

Van Strien J. W., (1988) Handedness and hemispheric laterality. Thesis Free University, Amsterdam, p. 33-45.

Udry J. R., Morris N. M., Kovenock, J. (1995) Androgen effects on women's gendered behaviour. J. Biosoc. Sci. 27: 359-368.

Received 24 April 1998, accepted 3 July 1998