



Sexual and regional permanent dopaminergic system impairment after prenatal and postnatal exposure to chlordimeform

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INTRODUCTION

Formamidine pesticides induce permanent effects on development of monoaminergic neurotransmitter systems. In this regard, chlordimeform induces permanent sex-dependent alterations of serotonergic and noradrenergic systems, but there is not information on dopaminergic system. The mechanisms that induce these effects are not known, but it has been suggested that these effects could be related to monoamine oxidase (MAO) inhibition. According to all above, we hypothesized that chlordimeform induced permanent alteration of dopaminergic system through a mechanism which is regardless of MAO inhibition.

METHODS

In order to confirm that formamidines induce permanent alterations of monoaminergic neurotransmitter systems regardless of MAO inhibition, the effects of maternal exposure to chlordimeform (5 mg/kg bw, orally on days 6–21 of pregnancy and 1–10 of lactation) on brain region dopamine levels of male and female offspring rats at 60 days of age were evaluated in brain regions by HPLC.

RESULTS

In male and female offspring, chlordimeform induced a significant decrease of dopamine levels in the prefrontal cortex, hippocampus and striatum, showing a gender interaction for these regions. Chlordimeform also caused a decrease of DOPAC levels in the striatum. Moreover, it induced an increase in the content of metabolites DOPAC and HVA in the hippocampus and an increase in the metabolite content of DOPAC in the striatum. Lastly, it increased the turnover of DA in the hippocampus and striatum and decreased the turnover of DA in frontal cortex.

CONCLUSIONS

The present findings indicate that maternal exposure to chlordimeform altered dopaminergic neurochemistry in their offspring in a region and sex-dependent way.

Table 1A. Tissue DA, DOPAC and HVA concentrations in male and female rat pups observed at 60 days of age after the exposure of dams to chlordimeform (5 mg/kg bw, orally on days 6 to 21 of pregnancy and 1 to 10 of lactation).

Tissue	DA (ng/g)		DOPAC (ng/g)		HVA (ng/g)		(DOPAC+HVA)/DA	
	Control group	Treated group (pups from treated dams)	Control group	Treated group (pups from treated dams)	Control group	Treated group (pups from treated dams)	Control group	Treated group (pups from treated dams)
HT	1266.34 ± 8.02	1306.23 ± 10.47	110.24 ± 1.71	111.28 ± 3.13	37.67 ± 0.89	37.92 ± 1.18	0.11 ± 0.00	0.11 ± 0.00
MB	1262.29 ± 27.37	1276.79 ± 26.49	60.22 ± 1.31	60.84 ± 0.84	34.00 ± 0.92	34.33 ± 1.09	0.07 ± 0.00	0.07 ± 0.00
CB	91.86 ± 0.69	92.84 ± 0.84	22.18 ± 0.38	22.33 ± 0.49	11.23 ± 0.30	11.24 ± 0.27	0.36 ± 0.01	0.36 ± 0.01
MO	304.44 ± 2.47	306.42 ± 4.52	21.19 ± 0.30	21.32 ± 0.32	1.03 ± 0.23	1.06 ± 0.22	0.11 ± 0.00	0.11 ± 0.00
BS	464.25 ± 4.26	469.47 ± 2.81	10.88 ± 0.26	10.94 ± 0.31	6.67 ± 0.08	6.73 ± 0.14	0.04 ± 0.00	0.04 ± 0.00
PFC	495.26 ± 2.28	378.02 ± 0.43	46.03 ± 0.43	33.54 ± 1.74	31.25 ± 1.39	22.52 ± 0.29	0.16 ± 0.00	0.15 ± 0.00
ST	7234.48 ± 22.25	8337.99 ± 43.89	821.85 ± 8.19	1118.99 ± 36.15	550.04 ± 11.69	456.62 ± 4.49	0.19 ± 0.00	0.23 ± 0.00
HC	814.42 ± 13.75	842.91 ± 28.34	32.85 ± 0.18	31.69 ± 0.41	4.69 ± 0.41	4.75 ± 0.40	0.03 ± 0.00	0.03 ± 0.00

HT: hypothalamus; MB: midbrain; CB: cerebellum; MO: medulla oblongata; BS: brainstem; PFC: prefrontal cortex; ST: striatum; HC: hippocampus.
Data represent means ± S.E.M. with values for males and females combined (n=12: 6 males + 6 females). Statistical significance is reported for the **P*<0.05, ***P*<0.01 and ****P*<0.001 levels compared with the control group.
%Percentage change from control values.
† Significant treatment × sex interaction.

Table 1B. Statistical analysis for tissue values with significant treatment × sex interaction.

Tissue	DA (ng/g)		DOPAC (ng/g)		HVA (ng/g)		(DOPAC+HVA)/DA		
	Control group	Treated group (pups from treated dams)	Control group	Treated group (pups from treated dams)	Control group	Treated group (pups from treated dams)	Control group	Treated group (pups from treated dams)	
PFC	Males	504.63 ± 3.24	431.46 ± 2.45***	46.01 ± 0.47	33.28 ± 0.31***	28.17 ± 0.23	22.83 ± 0.32***	0.13 ± 0.001***	0.14 ± 0.001***
	Females	486.49 ± 4.14	324.59 ± 3.43***	46.65 ± 0.44	29.51 ± 0.23***	34.32 ± 0.63	22.21 ± 0.20***	0.17 ± 0.00	0.15 ± 0.00*
ST	Males	7199.35 ± 18.99	6237.08 ± 11.46***	-	-	-	-	-	-
	Females	7271.10 ± 17.81	6438.90 ± 5.82***	-	-	-	-	-	-
HC	Males	483.85 ± 3.20	347.08 ± 4.26***	9.82 ± 0.08	10.89 ± 0.13***	4.79 ± 0.09	8.47 ± 0.10***	0.03 ± 0.00	0.06 ± 0.00*
	Females	545.00 ± 8.63	476.73 ± 3.91***	9.28 ± 0.19	12.47 ± 0.32***	4.69 ± 0.06	6.64 ± 0.10***	0.03 ± 0.00	0.04 ± 0.00*

PFC: prefrontal cortex. Other tissue values were not evaluated because of the lack of treatment × sex interaction. Values are mean ± S.E.M.: control animals (n= 6 males, n= 6 females); treated group (n= 6 males, n= 6 females). Statistical significance is reported for the **P*<0.05 and ****P*<0.001 levels compared with the control group within each sex as determined by one-way ANOVA, followed by the Student's *t* test.
%Percentage change from control values.