



Permanent sexual and regional noradrenergic system impairment after prenatal and postnatal exposure to chlordimeform



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INTRODUCTION

Formamidines pesticides have been described to induce permanent effects on development of monoaminergic neurotransmitter systems. The mechanisms that induce these effects are not known but it has been suggested that these effects could be related to monoamino oxidase (MAO) inhibition. Chlordimeform is a formamidine pesticide, which is a very weak inhibitor of MAO although it has been described to induce permanent and sex dependent alterations of serotonergic system. According to all above, we hypothesized that chlordimeform induced permanent alteration of noradrenergic 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 noradrenaline levels of male and female offspring rats at 60 days of age were evaluated in brain regions by HPLC.

RESULTS

The results showed that chlordimeform induced a significant decrease of noradrenaline levels in the prefrontal cortex and striatum, showing an interaction by sex for these regions. Chlordimeform also caused a decrease of MHPG and HVA metabolites levels in the prefrontal cortex and striatum. Lastly, it decreased the turnover of NA in frontal cortex and striatum.

CONCLUSIONS

Our results indicate that maternal exposure to chlordimeform altered noradrenergic system in their offspring in a region and sex dependent way, and confirm that other mechanisms different from MAO inhibition are implicated.

Table 1. Tissue NA and MHPG 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	NA (ng/g)		MHPG (ng/g)		MHPG/NA	
	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	1338,98± 10,80	1355,06± 17,17	48,47± 0,75	49,06± 0,79	0,04± 0,00	0,04± 0,00
MB	579,97± 15,72	587,54± 20,84	45,00± 0,67	45,50± 0,62	0,08± 0,00	0,08± 0,00
CB	232,96± 3,39	235,09± 5,97	24,40± 0,55	24,54± 0,57	0,10± 0,00	0,10± 0,00
MO	244,22± 2,77	244,00± 3,98	28,45± 0,25	28,67± 0,39	0,12± 0,00	0,12± 0,00
BS	420,66± 8,99	426,74± 7,01	23,51± 0,33	23,84± 0,43	0,06± 0,00	0,06± 0,00
PFC	234,37± 4,08	180,77± 6,69	52,74± 0,45	37,64± 1,51	0,23± 0,00	0,21± 0,00
ST	165,73± 3,56	139,80± 6,09	81,01± 0,68	59,69± 3,66	0,49± 0,01	0,43± 0,01
HC	242,26± 7,86	245,86± 9,21	34,78± 0,30	35,04± 0,30	0,14± 0,00	0,14± 0,01

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 2. Statistical analysis for tissue values with significant treatment × sex interaction.

Tissue	Sex	NA (ng/g)		MHPG (ng/g)		MHPG/NA	
		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	243,71 ± 1,15	196,29 ± 1,05***	52,43 ± 0,33	41,13 ± 0,16***	0,22 ± 0,001*	0,21 ± 0,001*
	Females	225,04 ± 0,60	165,25 ± 0,95***	53,05 ± 0,54	34,15 ± 0,33***	0,24 ± 0,003***	0,21 ± 0,003***
ST	Males	173,40 ± 1,19	154,01 ± 0,80***	81,98 ± 0,68	68,21 ± 0,60***	0,47 ± 0,01	0,44 ± 0,00***
	Females	158,07 ± 1,71	125,59 ± 0,39***	80,04 ± 0,40	51,18 ± 0,34***	0,51 ± 0,01	0,41 ± 0,00***

PFC: prefrontal cortex. Other tissue values were not evaluated because of the lack of treatment × sex interactions. 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*<0.01 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.