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Neuroendocrine effects of styrene on occupationally exposed workers

by Antonio Mutti, MD,¹ Pier P Vescovi, MD,² Maurizio Falzoi, MD,¹ Giuseppe Arfini, MD,¹ Giorgio Valenti, MD,² Innocente Franchini, MD¹

MUTTI A, VESCOVI PP, FALZOI M, ARFINI G, VALENTI G, FRANCHINI I. Neuroendocrine effects of styrene on occupationally exposed workers. *Scand J Work Environ Health* 10 (1984) 225–228. The serum levels of prolactin (PRL), human growth hormone (HGH), thyroid-stimulating hormone (TSH), and the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were measured in 30 females exposed to about 130 (range 65–300) ppm of styrene in the air and in 30 age-matched referents to show whether styrene exposure influences the dopaminergic tuberoinfundibular system (TIDA). The exposed subjects' serum levels of PRL were more than double the reference values and were significantly related to the urinary excretion of styrene metabolites, ie, to the sum of mandelic acid (MA) and phenylglyoxylic acid (PGA) in the "next-morning" urine spot sample. Such a relationship still proved to be statistically significant after the removal of the effects of age and duration of exposure with the method of partial correlation. The serum concentrations of HGH in the exposed workers were also higher than in the reference group. Though within the reference levels, the TSH values of the exposed subjects were significantly related to the urinary excretion of MA and PGA. These results are consistent with the dose-dependent depletion in tuberoinfundibular dopamine after experimental styrene exposure of rabbits.

Key terms: dopamine, gonadotropins, growth hormone, prolactin, thyroid-stimulating hormone, reinforced plastics.

By using electrophysiological techniques (10, 12, 21, 22) and neuropsychological methods (3, 4, 8, 9, 13, 19), several field and experimental studies have given evidence of styrene toxicity to the central nervous system. Exposure-effect and exposure-response relations have been found for visuomotor and visuoperceptive abilities, vigilance, and memory functions (10, 16, 17).

The neurochemical and pathophysiological bases for styrene-induced central nervous dysfunction have not yet been fully elucidated. Some evidence is available of biochemical changes leading to abnormal brain protein metabolism, after repeated exposures of rats to styrene vapors (20). A possible interference of styrene and/or its metabolites with the concentration and activity of brain catecholamines has also been suggested (1, 11, 15). These different mechanisms might coexist and account for some mild chronic abnormalities, eg, abnormal electroencephalographic findings, and the acute behavioral effects of styrene exposure on humans.

The present study was aimed at evaluating the possible interference of styrene or its metabolites with

the activity of the tuberoinfundibular dopaminergic system (TIDA) in humans. Such an effect was indirectly investigated with measurements of some neuroendocrine parameters, namely, serum prolactin (PRL), human growth hormone (HGH), thyroid-stimulating hormone (TSH), and gonadotropins [follicle-stimulating hormone (FSH) and luteinizing hormone (LH)].

Subjects and methods

Subjects

The exposed group was composed of 30 female workers employed in two factories manufacturing glass-fiber reinforced boats and silos. Their mean age was 28.6 (SD 12.7) years, and their exposure time to styrene vapors averaged 6.2 (SD 4.6) years. The reference group was composed of 30 age-matched females selected from a pool of factory workers living in the same area as the styrene-exposed subjects and not exposed to industrial chemicals. Their mean age was 29.2 (SD 10.5) years. Both the exposed and the reference subjects were healthy workers, with no history or clinical signs of endocrine and neurological diseases. Information about the menstrual cycle was collected with a questionnaire. Only those subjects in the proliferative phase (between the 5th and the 15th day of the cycle) were admitted to the study. None of them had been receiving psychotropic drugs.

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Table 1. Neuroendocrine effects of styrene exposure. (PRL = serum prolactin, TSH = thyroid-stimulating hormone, HGH = human growth hormone, FSH = follicle-stimulating hormone, LH = luteinizing hormone)

Group	PRL (pmol/l)	TSH (mIU/l)	HGH (pmol/l)	FSH (mIU/l)	LH (mIU/l)
Exposed					
Mean	633**	2.3	.	.	.
SD	372	1.3	.	.	.
Median	.	.	520*	10.1	13.4
Range	.	.	65—1,422	3.6—118.8	9.2—107.7
Reference					
Mean	313	2.7	.	.	.
SD	175	1.8	.	.	.
Median	.	.	329	8.8	11.7
Range	.	.	67—1,198	1.6—18.7	8.0—42.7

* $p < 0.05$ (Mann-Whitney U-test), ** $p < 0.001$ (Student's t-test, two-tailed).

Table 2. Simple and partial correlation coefficients between styrene exposure and those neuroendocrine variables normally distributed among the exposed group. (PRL = serum prolactin, TSH = thyroid-stimulating hormone, MA = mandelic acid, PGA = phenylglyoxylic acid)

	PRL	TSH
Zero order		
Styrene metabolites (MA + PGA)	0.573***	0.321*
Exposure time (years)	-0.407*	-0.122
Age (years)	-0.450**	-0.197
Control for exposure time		
Styrene metabolites (MA + PGA)	0.575***	0.310*
Control for age (years)		
Styrene metabolites (MA + PGA)	0.617***	0.317*
Exposure time (years)	-0.158	0.013
Control for age (years) and styrene metabolites (MA + PGA)		
Exposure time (years)	-0.100	0.058
Control for age (years) and exposure time (years)		
Styrene metabolites (MA + PGA)	0.609***	0.322*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Exposure

The urinary excretions of mandelic acid (MA) and phenylglyoxylic acid (PGA) in the "next-morning" urine spot samples were used as biological indicators of internal dose. Exposure intensity was rather high, as measured by the sum of MA and PGA, the mean value being 580 (SD 290) mmol/mol of creatinine. On the basis of the relationship between environmental and biological exposure test measurements, such values correspond to an 8-h time-weighted concentration of about 130 (range 65—300) ppm of styrene in the air (6).

Methods

The urine samples were collected immediately before the venipuncture for blood sampling. Urine, adjusted to pH 2 with 1 mol of hydrochloric acid, was stored at -20°C up to the time of analysis, which was carried out in the following 2 d by high-performance liquid chromatography according to the method described

elsewhere (7). The styrene metabolite levels were then adjusted for creatinine, which was measured by the Jaffe reaction with a Technicon Auto Analyzer. Ten-milliliter venous blood samples were taken while the subjects were seated before they started work in the morning (from 0800 to 0900). Serum was centrifuged as soon as possible and stored at -20°C up to the time of analysis, which was performed in triplicate within a month. Commercially available kits (Biodata, Milan) were used for the radioimmunoassay of PRL, HGH, TSH, FSH, and LH.

Statistical analysis was carried out with the SPSS programs (18). After the testing for a normal distribution of both the referents' and the exposed subjects' hormone levels with the use of the nonparametric Kolmogorov-Smirnov test, any significant differences between the two groups were assessed by the Student's t-test (for PRL & TSH) or the Mann-Whitney U-test (for HGH, FSH, & LH). Pearson's correlation coefficients were used to identify any relationship between independent variables and serum hormone levels.

The partial correlation method was used to remove the effects of age and duration of exposure from the dose-effect relationships.

Results

Table 1 shows the comparison between the exposed subjects and the referents. The serum levels of PRL and HGH were about double the reference values, the difference being statistically significant. No difference could be detected for TSH and the gonadotropins, although the latter were slightly higher in the exposed subjects than in the referents.

Table 2 summarizes Pearson's correlation coefficients between the independent variables and those neuroendocrine variables normally distributed among the exposed group. The partial correlation coefficients are also reported after control for the possible effects of any interrelationship between the independent variables. The serum levels of PRL and TSH were significantly related to the urinary excretion of styrene metabolites, ie, to the sum of MA and

Figure 1. Relationship between the urinary excretion of mandelic acid (MA) and phenylglyoxylic acid (PGA) in the "next-morning" spot sample and the basal serum level of prolactin (PRL).

Figure 2. Relationship between the urinary excretion of mandelic acid (MA) and phenylglyoxylic acid (PGA) in the "next-morning" spot sample and the basal serum level of thyroid-stimulating hormone (TSH).

PGA in the "next-morning" urine spot sample. Both age and exposure time were negatively related to serum PRL. After control for age and exposure time, the PRL and TSH levels still proved to be related to the intensity of styrene exposure. After control for age and exposure intensity, the negative relationship between duration of exposure and serum PRL was not statistically significant.

Figure 1 shows the correlation between serum PRL and the sum of MA and PGA in the "next-morning" urine sample. Though not statistically different as compared to the reference values, the TSH serum levels also correlated with the urinary excretion of styrene metabolites (figure 2).

Discussion

The role of TIDA neurons in the control of pituitary hormone secretions has been stressed by several studies dealing with the diagnostic or therapeutic use of dopamine agonist and antagonist drugs in subjects with hypophyseal adenoma. It is well established that, in a number of neurotransmitters and neuromodulators, the dopaminergic pathways have an inhibitory function on pituitary secretion. PRL secretion is directly controlled by the activity of TIDA neurons, whereas the more complex modulation of HGH, TSH, and LH is indirectly performed through the inhibition of hypothalamic neurons secreting somatostatin (SRIF), thyrotropin-releasing hormone (TRH), and LH-releasing hormone (LH-RH) (14).

The results of the present study strongly support the hypothesis of an interference of styrene exposure with TIDA activity in humans. To our knowledge, this is the first paper dealing with the neuroendocrine effects of styrene exposure. Thus no comparison is

possible with the available findings in the literature. A previous experimental study had given evidence of a dose-dependent depletion in striatal and tuberoinfundibular dopamine after the acute styrene exposure of rabbits (15). A selective inhibition of brain dopamine receptors after repeated oral administration of styrene to rats has also been reported (1). Though the pathophysiological bases of such effects are not yet fully understood, the available experimental data are consistent with the results we have obtained with humans.

We speculate that a styrene metabolite, possibly PGA, might be aminated to the α -amino acid phenylglycine. The latter would compete with dopamine for vesicular storage capacity, as do some biogenic amines, namely, phenylethylamines (5).

Serum PRL is the most sensitive indicator of impaired TIDA activity. Moreover, it is directly controlled by dopaminergic neurons, which are further stimulated by increased serum PRL through a feedback mechanism. By contrast, the indirect inhibitory role of dopamine on TSH release, which is mediated by the control of TRH secretion, would make this hormonal response less sensitive to TIDA activity. The modulatory role of dopamine upon the pituitary secretion of HGH and gonadotropins requires an even more complex interaction with other neurotransmitters, neuromodulators, or hormones. Moreover, the variability of HGH and gonadotropins may be explained in part by the fact that only one blood sample was drawn. This occurrence might affect the reliability of the HGH and LH values, though both the exposed and reference subjects were examined under the same conditions.

The styrene-induced neuroendocrine effects are mostly due to acute exposure, the hormone levels not being influenced by the duration of exposure, after

control for age and exposure intensity with the partial correlation method.

Owing to the lack of specificity, the neuroendocrine parameters cannot be recommended for the biological monitoring of occupational exposure to styrene. Moreover, such effects on hypophyseal secretion were observed at exposure levels much higher than 50 ppm, ie, levels higher than the current threshold limit value recommended by the American Conference of Governmental Industrial Hygienists (2).

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