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Short Communication

Multiple metals predict prolactin and thyrotropin (TSH) levels in men

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ABSTRACT

Exposure to a number of metals can affect neuroendocrine and thyroid signaling, which can result in adverse effects on development, behavior, metabolism, reproduction, and other functions. The present study assessed the relationship between metal concentrations in blood and serum prolactin (PRL) and thyrotropin (TSH) levels, markers of dopaminergic, and thyroid function, respectively, among men participating in a study of environmental influences on male reproductive health. Blood samples from 219 men were analyzed for concentrations of 11 metals and serum levels of PRL and TSH. In multiple linear regression models adjusted for age, BMI and smoking, PRL was inversely associated with arsenic, cadmium, copper, lead, manganese, molybdenum, and zinc, but positively associated with chromium. Several of these associations (Cd, Pb, Mo) are consistent with limited studies in humans or animals, and a number of the relationships (Cr, Cu, Pb, Mo) remained when additionally considering multiple metals in the model. Lead and copper were associated with non-monotonic decrease in TSH, while arsenic was associated with a dose-dependent increase in TSH. For arsenic these findings were consistent with recent experimental studies where arsenic inhibited enzymes involved in thyroid hormone synthesis and signaling. More research is needed for a better understanding of the role of metals in neuroendocrine and thyroid function and related health implications.

1. Introduction

A number of metals can accumulate in the brain (Popek et al., 2006; Hu, 2000) and affect neuroendocrine function, including adverse impacts on the dopaminergic system and related behavioral abnormalities (Jones and Miller, 2008). Dopamine, along with other factors (including thyrotropin releasing hormone (TRH)), regulate the release of prolactin (PRL). PRL is a protein hormone that serves a number of vital functions involving metabolism, reproduction, and maintenance of homeostasis in immune responses, osmotic balance, and angiogenesis (Ben-Jonathan et al., 2008; Freeman et al., 2000), and is becoming increasingly used as a measure of neuroendocrine/dopaminergic function in environmental and occupational epidemiology studies. For example, environmental levels of cadmium and mercury were inversely associated with PRL levels in children (de Burbure et al., 2006). Lead was inversely associated with PRL among men (Telisman et al., 2007) and pregnant women (Takser et al., 2005) without occupational lead exposure, but positively associated with PRL among occupationally exposed men (Lucchini et al., 2000; Govoni et al., 1987). Occupational exposure to manganese has also been positively associated with PRL (Ellingsen et al., 2007, 2003), as has environmental manganese exposure among adults (Montes et al., 2008) and neonates (Takser et al., 2004).

In addition to regulating PRL, dopamine is also involved in thyrotropin (TSH) activity and TSH subunit secretion (Soldin and Aschner, 2007), though TSH is primarily controlled by TRH. TSH stimulates secretion of thyroid hormones, which are vital for a number of physiological processes including metabolism, reproduction, and neurodevelopment. There is limited evidence that a number of metals may affect thyroid function, including inorganic arsenic (Davey et al., 2008), cadmium (Iijima et al., 2007), lead (Dundar et al., 2006), manganese (Soldin and Aschner, 2007), and organic mercury, (Soldin et al., 2008), as well as copper, selenium, and zinc (Arthur and Beckett, 1999). Alterations in circulating thyroid hormone or TSH levels in relation to exposure may be due to effects at different levels of the hypothalamus-pituitary-thyroid axis, and/or may be a result of altered thyroid hormone transport

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and peripheral metabolism/deactivation (Zoeller et al., 2007; Boas et al., 2006). In the present study we assessed blood metal concentrations and serum PRL and TSH levels among men participating in a larger study of environmental factors in male reproduction.

2. Methods

2.1. Subject recruitment

The study cohort has been described in a previous report (Wirth et al., 2007). Briefly, men aged 18–55 were recruited from two Michigan infertility clinics. Men taking hormone therapy or who had diabetes, thyroid or adrenal disorders, or other medical conditions associated with infertility were not eligible for enrollment. Since couples may present at the clinics for problems relating to male and/or female fertility problems, participants included fertile men and men with a range of fertility problems. The protocols of the study were approved by the committees on research ethics at all participating institutions.

2.2. Hormone measurement

Blood samples were collected from participants during a morning clinic visit. PRL and TSH were measured by solid phase, two site, chemiluminescent enzyme immunometric assay using the Immulite Assay System (Diagnostic Products Corp., Los Angeles, CA). The intra- and inter-assay variabilities, expressed as coefficient of variations, were 6.2 and 8.5 for PRL and 7.1 and 11.1 for TSH. Assay sensitivities were 0.5 ng/mL for PRL and 0.004 μIU/mL for TSH.

2.3. Measurement of metals

Whole venous blood was collected using stainless steel needles into 2 mL plastic tubes containing EDTA (prescreened for mercury, cadmium, and lead). Samples were analyzed for arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), lead (Pb), manganese (Mn), total mercury (Hg), molybdenum (Mo), selenium (Se), thallium (Tl), and zinc (Zn) using a Perkin Elmer Elan DRC plus Inductively Coupled Plasma Mass Spectrometer (ICP-MS). The limits of detection (LOD) for the blood metal levels were as follows: As, 4.0 μg/L; Cd, 0.2 μg/L; Cu, 2.0 μg/L; Cr, 0.5 μg/L; Pb, 0.3 μg/dL; Mn, 1.0 μg/L; Hg, 0.2 μg/L; Mo, 1.0 μg/L; Se, 5 μg/L; Tl, 0.1 μg/L; and Zn, 50 μg/L.

2.4. Statistical analysis

Data analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Due to the high proportion of samples below the LOD for a number of metals, these variables were categorized into groups. At least 3 groups were formed for each metal to investigate dose-dependent relationships. Metals with greater then 75% of samples greater than the LOD were categorized into quartiles. For the other metals grouping cutpoints were determined by the percentage of samples above the LOD. The low group consisted of values below the LOD for each metal, while the medium and high groups were made up of equal-sized bins among the detected values. The association between metal exposure categories and PRL or TSH levels were assessed by multiple linear regression in separate models for each metal. PRL and TSH levels were skewed right and transformed by the natural logarithm in the data analysis. Full linear regression models were then constructed when considering all metals along with the other covariates (age, BMI, race, income, season, and smoking status). The backward elimination procedure was utilized and alpha was set at 0.1 for variables to be retained in the model. Covariates not retained in the final model were then added individually to further explore evidence of confounding (i.e. causing $>10\%$ change in metal effect estimate). Finally, evidence of interaction between metals in association with hormone levels was explored by comparing effect estimates of one metal while stratifying by blood levels of another metal.

3. Results

Among the 219 men who contributed data on both hormone and metal concentrations, the median (25th, 75th) PRL and TSH values were 9.8 ng/mL (7.4, 12.4) and 1.32 μIU/mL (0.96, 1.83), respectively. The distributions of blood metal concentrations among these men were representative of low-level environmental exposures and have been previously reported (Meeker et al., 2008). Cutoff values for exposure categories used in the data analysis are presented in Table 1, along with linear regression results for each metal separately in crude analyses and when adjusted for age, BMI, and smoking status. In the adjusted analysis chromium was positively associated with PRL, while arsenic, cadmium, copper, lead, manganese, molybdenum, and zinc were all inversely associated with PRL. Copper and lead were associated with non-monotonic declines in TSH, whereas arsenic and thallium were suggestively associated with increased TSH.

Table 2 presents the results from the multivariable analysis that considered all measured metals simultaneously. PRL remained positively associated with chromium and inversely associated with copper, lead, and molybdenum, as well as with age, race, and smoking. The inverse associations for lead and molybdenum followed a dose-dependent pattern. Cadmium, manganese, and zinc, which were inversely related to PRL in the multivariable models for individual metals, were not retained in the final model. In the full TSH model arsenic was associated with a monotonic increase in TSH, and copper and lead were associated with non-monotonic decreases in TSH. Finally, in secondary analyses there was no evidence for interactions between metals in association with PRL or TSH. Results were also similar to those presented in Tables 1 and 2 when excluding smokers from the analyses.

4. Discussion

We found that multiple metals were associated with PRL and TSH levels in men, but the direction of the association was not consistent among metals, which may potentially suggest differing sites and mechanisms of action that manifest as altered PRL or TSH levels. Because multiple comparisons were made, some of the associations may be due to chance. In addition, there may have been unmeasured co-exposures that may have confounded our findings (e.g. simultaneous exposure to arsenic and iodine from seafood consumption). However, a number of our findings are consistent with previous human, animal, or *in vitro* studies.

Our finding of an inverse association between lead and PRL is consistent with a recent study among 240 Croatian men with no occupational exposure to metals, though exposure levels in that study were somewhat higher than those in the present study (Telisman et al., 2007). Likewise, an inverse relationship between lead and PRL was reported among pregnant women in Canada (Takser et al., 2005). de Burbure et al. (2006) also reported an inverse association between lead and PRL in children, but only as an interaction with cadmium. In addition to lead, the present study also found an inverse relationship between copper and PRL. This is inconsistent with previous studies among men in Croatia that did not report an association between copper and PRL (Telisman et al., 2000, 2007; Jurasovic et al., 2004). To our knowledge this is the first human study to assess PRL in relation to molybdenum and chromium, where PRL was inversely associated with molybdenum and positively associated with chromium. These findings are consistent with a rat study that reported an inverse association between molybdenum and PRL (Bandyopadhyay et al., 1981), but inconsistent with a recent study that reported hexavalent chromium caused adverse effects on the hypothalamus and anterior pituitary and resulted in reduced serum PRL levels in rats (Quinteros et al., 2007). However, we measured only total chromium. The proportion of exposure to chromium in the hexavalent form in these men may be expected to be low and/or quickly reduced to trivalent chromium upon uptake.

Although cadmium was not retained in the final PRL model that considered other metals, our finding of an inverse association between cadmium and PRL in the initial multivariable model was consistent with previous human studies among Croatian men with potential occupational exposure (Telisman et al., 2000),

Table 1
Crude and adjusted[a] regression coefficients for change in serum hormone level associated with metal exposure groups.

Metal percentiles	Corresponding blood levels	Prolactin[b]		TSH[b,c]	
		Crude	Adjusted[a]	Crude	Adjusted[a]
Arsenic					
<25th	<5.8 μg/L	0	0	0	0
25th–50th	5.8–8.1	−0.23 (−0.39, −0.07)	−0.25 (−0.40, −0.09)	−0.04 (−0.24, 0.16)	−0.07 (−0.27, 0.14)
50th–75th	8.1–10.0	−0.24 (−0.40, −0.09)	−0.24 (−0.39, −0.09)	0.04 (−0.16, 0.24)	0.03 (−0.17, 0.23)
>75th	>10.0	−0.33 (−0.49, −0.17)	−0.33 (−0.49, −0.18)	0.14 (−0.06, 0.24)	0.12 (−0.09, 0.32)
p for trend		0.0001	<0.0001	0.13	0.16
Cadmium					
<50th	<0.2 μg/L	0	0	0	0
50th–75th	0.2–0.4	−0.15 (−0.29, −0.01)	−0.13 (−0.26, 0.01)	0.02 (−0.15, 0.20)	0.02 (−0.16, 0.20)
>75th	>0.4	−0.24 (−0.38, −0.10)	−0.15 (−0.33, 0.02)	0.01 (−0.17, 0.18)	0.07 (−0.15, 0.29)
p for trend		0.0004	0.04	0.90	0.56
Chromium					
<70th	<0.5 μg/L	0	0	0	0
70th–85th	0.5–0.9	−0.04 (−0.19, 0.12)	−0.01 (−0.17, 0.14)	0.02 (−0.18, 0.22)	0.02 (−0.18, 0.23)
>85th	>0.9	0.25 (0.09, 0.41)	0.23 (0.08, 0.39)	0.02 (−0.18, 0.22)	0.03 (−0.17, 0.23)
p for trend		0.01	0.01	0.80	0.75
Copper					
<25th	<817 μg/L	0	0	0	0
25th–50th	817–887	−0.14 (−0.30, 0.02)	−0.12 (−0.28, 0.03)	−0.16 (−0.36, 0.04)	−0.16 (−0.37, 0.03)
50th–75th	887–974	−0.25 (−0.41, −0.09)	−0.25 (−0.41, −0.09)	−0.15 (−0.36, 0.05)	−0.20 (−0.41, 0.01)
>75th	>974	−0.21 (−0.37, −0.05)	−0.14 (−0.31, 0.03)	−0.10 (−0.30, 0.10)	−0.15 (−0.36, 0.07)
p for trend		0.005	0.04	0.38	0.15
Lead					
<25th	<1.1 μg/dL	0	0	0	0
25th–50th	1.1–1.5	−0.11 (−0.26, 0.04)	−0.04 (−0.19, 0.11)	−0.14 (−0.33, 0.05)	−0.17 (−0.37, 0.02)
50th–75th	1.5–2.0	−0.28 (−0.44, −0.12)	−0.22 (−0.38, −0.06)	−0.35 (−0.55, −0.15)	−0.37 (−0.57, −0.16)
>75th	>2.0	−0.29 (−0.44, −0.14)	−0.20 (−0.36, −0.05)	−0.16 (−0.35, 0.03)	−0.18 (−0.38, −0.02)
p for trend		<0.0001	0.002	0.03	0.03
Manganese					
<25th	<10.0 μg/L	0	0	0	0
25th–50th	10.0–12.5	−0.13 (−0.28, 0.01)	−0.17 (−0.31, −0.03)	0.01 (−0.17, 0.18)	0.003 (−0.18, 0.18)
50th–75th	12.5–14.0	−0.33 (−0.50, −0.16)	−0.30 (−0.47, −0.14)	−0.10 (−0.32, 0.11)	−0.10 (−0.32, 0.12)
>75th	>14.0	−0.12 (−0.29, 0.05)	−0.14 (−0.30, 0.02)	−0.05 (−0.26, 0.16)	−0.12 (−0.27, 0.15)
p for trend		0.03	0.03	0.43	0.40
Mercury					
<25th	<0.6 μg/L	0	0	0	0
25th–50th	0.6–1.1	0.08 (−0.09, 0.24)	0.01 (−0.09, 0.23)	−0.05 (−0.25, 0.15)	−0.06 (−0.26, 0.14)
50th–75th	1.1–2.3	−0.06 (−0.21, 0.10)	−0.05 (−0.21, 0.10)	−0.07 (−0.26, 0.13)	−0.06 (−0.25, 0.14)
>75th	>2.3	−0.01 (−0.17, 0.15)	0.04 (−0.12, 0.19)	0.06 (−0.13, 0.25)	0.08 (−0.12, 0.28)
p for trend		0.58	0.99	0.64	0.56
Molybdenum					
<70th	<1.0 μg/L	0	0	0	0
70th–85th	1.0–1.5	−0.08 (−0.24, 0.08)	−0.11 (−0.26, 0.05)	−0.02 (−0.22, 0.17)	−0.02 (−0.22, 0.18)
>85th	>1.5	−0.13 (−0.30, 0.04)	−0.20 (−0.36, −0.03)	−0.01 (−0.21, 0.20)	0.01 (−0.20, 0.22)
p for trend		0.10	0.01	0.89	0.98
Selenium					
<25th	<171 μg/L	0	0	0	0
25th–50th	171–182	−0.05 (−0.21, 0.11)	−0.04 (−0.20, 0.11)	0.02 (−0.18, 0.21)	0.01 (−0.19, 0.21)
50th–75th	182–198	−0.06 (−0.22, 0.11)	−0.07 (−0.23, 0.09)	0.13 (−0.70, 0.33)	0.12 (−0.08, 0.33)
>75th	>198	−0.07 (−0.24, 0.09)	−0.09 (−0.25, 0.06)	0.07 (−0.13, 0.27)	0.07 (−0.13, 0.27)
p for trend		0.38	0.22	0.32	0.32
Thallium					
<50th	<1.0 μg/L	0	0	0	0
50th–75th	1.0–1.1	−0.05 (−0.19, 0.09)	−0.06 (−0.20, 0.07)	0.02 (−0.15, 0.19)	0.02 (−0.15, 0.19)
>75th	>1.1	−0.11 (−0.25, 0.03)	−0.09 (−0.23, 0.05)	0.16 (−0.02, 0.33)	0.15 (−0.02, 0.33)
p for trend		0.13	0.18	0.10	0.11
Zinc					
<25th	<6169 μg/L	0	0	0	0
25th–50th	6169–6770	−0.05 (−0.21, 0.11)	−0.07 (−0.22, 0.09)	0.14 (−0.09, 0.38)	0.13 (−0.07, 0.33)
50th–75th	6770–7294	0.04 (−0.12, 0.21)	−0.002 (−0.16, 0.15)	0.13 (−0.11, 0.36)	0.13 (−0.07, 0.33)
>75th	>7294	−0.16 (−0.32, 0.01)	−0.21 (−0.37, −0.05)	0.11 (−0.13, 0.34)	0.11 (−0.09, 0.31)
p for trend		0.15	0.03	0.32	0.19

[a] Adjusted for age, BMI, and current smoking.
[b] ln-transformed.
[c] One extreme low TSH value (0.05 μIU/mL) and one extreme high TSH value (54 μIU/mL) were removed. These values were greater than 3 standard deviations from the mean following ln-transformation.

Table 2
Final linear regression models[a] for hormone levels when considering multiple metals and other covariates.

Variable	Regression coefficient (95%CI)	p-value (for trend where appropriate)
Prolactin[b]		
Chromium		
70th–85th	−0.001 (−0.15, 0.15)	
>85th	0.15 (−0.01, 0.31)	0.05
Copper		
25th–50th	−0.09 (−0.25, 0.07)	
50th–75th	−0.23 (−0.38, −0.07)	
>75th	−0.15 (−0.32, 0.01)	0.01
Lead		
25th–50th	−0.06 (−0.21, 0.09)	
50th–75th	−0.22 (−0.38, −0.06)	
>75th	−0.26 (−0.42, −0.10)	0.0002
Molybdenum		
70th–85th	−0.08 (−0.23, 0.08)	
>85th	−0.17 (−0.33, −0.01)	0.03
Age		
Year increase	−0.01 (−0.02, −0.002)	0.02
Race[c]		
White	−0.17 (−0.31, −0.04)	0.004
Smoking Status[d]		
Current smoker	−0.16 (−0.30, −0.03)	0.03
TSH[b,e]		
Arsenic		
25th–50th	0.07 (−0.15, 0.29)	
50th–75th	0.16 (−0.05, 0.38)	
>75th	0.25 (0.03, 0.47)	0.02
Copper		
25th–50th	−0.16 (−0.37, 0.05)	
50th–75th	−0.23 (−0.45, −0.02)	
>75th	−0.18 (−0.41, 0.05)	0.04
Lead		
25th–50th	−0.15 (−0.34, 0.04)	
50th–75th	−0.35 (−0.56, −0.15)	
>75th	−0.19 (−0.38, 0.004)	0.02
BMI		
Unit increase	0.01 (−0.002, 0.02)	0.07

[a] Backward elimination; same results obtained with forward selection and stepwise procedures.
[b] Variable ln-transformed.
[c] Reference group = non-white.
[d] Reference group = non-smoker.
[e] One extreme low TSH value (0.05 μIU/mL) and one extreme high TSH value (54 μIU/mL) were removed. These values were greater than 3 standard deviations from the mean following ln-transformation.

among Croatian men with no specific occupational exposure to metals (Jurasovic et al., 2004), and among children (de Burbure et al., 2006). Conversely, manganese, which was also inversely associated with PRL in our initial multivariable model prior to consideration of other metals, was positively associated with PRL in human studies of neonates (Takser et al., 2004), adults (Montes et al., 2008), and occupationally exposed men (Ellingsen et al., 2003, 2007).

TSH was positively associated with arsenic in the present study, which is consistent with the experimental data demonstrating that arsenic trioxide inhibits thyroid peroxidase activity (TPO) in vitro (Palazzolo and Jansen, 2008). TPO is the major enzyme involved in thyroid hormone synthesis, and TPO inhibition likely results in declined thyroid hormone levels, which, through feedback mechanisms, would result in increased TSH. Another recent study reported that low doses of arsenic disrupted thyroid hormone receptor-mediated gene regulation and amphibian developmental processes that are mediated by thyroid hormones (Davey et al., 2008). Finally, we found non-monotonic inverse relationships between TSH and copper and lead. Human studies of copper and thyroid function are lacking and those for lead have been inconsistent (Dundar et al., 2006), though our findings of declined TSH in relation to lead are consistent with findings among women (but not men) in a recent study (Abdelouahab et al., 2008) and may be indicative of altered pituitary function (Gustafson et al., 1989).

In conclusion, we found that a number of metals were associated with PRL and TSH levels in men. More research, including human studies with more detailed markers of dopaminergic and thyroid function, is needed to further explain the potential influence of metals on these systems.

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