



Mercury as a possible link between maternal obesity and autism spectrum disorder



Anatoly V. Skalny^{a,b,c}, Margarita G. Skalnaya^d, Geir Bjørklund^e, Alexandr A. Nikonorov^{b,f}, Alexey A. Tinkov^{a,b,c,f,*}

^a All-Russian Research Institute of Medicinal and Aromatic Plants (VILAR), Moscow, Russia

^b Orenburg State University, Orenburg, Russia

^c Yaroslavl State University, Yaroslavl, Russia

^d Russian Society of Trace Elements in Medicine, Moscow, Russia

^e Council for Nutritional and Environmental Medicine, Mo i Rana, Norway

^f Orenburg State Medical University, Orenburg, Russia

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ABSTRACT

The incidence of both obesity and autism spectrum disorders (ASD) has dramatically increased during the last decades. Moreover, the most recent studies have revealed increased risk of ASD in offspring of overweight and obese women. However, the mechanisms of association between ASD and maternal obesity are unknown. Taking into account the existing data indicating the association between mercury (Hg) exposure and development of obesity and ASD, we hypothesize that Hg may serve as an additional link between maternal obesity and ASD. In particular, it is supposed that obesity is associated with excessive accumulation of Hg in the maternal organism. After conception, the fetus is developing in the conditions of Hg overload within the body of obese women thus predisposing to the development of ASD. The proposed hypothesis may be confirmed by the existing data. In particular, previous studies demonstrated that overweight and obese persons are characterized by a significantly higher level of Hg in hair, blood and urine than the lean ones. Therefore, an obese organism is characterized by elevated Hg burden that may be transferred to the fetus during pregnancy. Moreover, multiple studies have demonstrated a tight association between maternal and children Hg status being indicative of placental transfer of metal from maternal organism to offspring. Finally, a growing body of data indicates the influence of Hg exposure and Hg status on the risk of ASD in children. However, additional experimental and clinical studies are required to prove the hypothesis and provide novel data on the role of Hg in maternal obesity-associated ASD development. In particular, the contribution of Hg to ASD development in children from obese mothers should be determined. If a significant role of Hg in maternal obesity ASD risk will be confirmed, this will open additional perspectives of risk modification. Taking into account the universal mechanisms of Hg toxicity, transport, and accumulation, further preventive actions may be undertaken to reduce the risk of Hg toxicity and Hg-associated ASD development. In particular, it is supposed that the use of Hg chelators (like N,N'-bis-(2-mercaptoethyl)isophthalamide, NMBI), antioxidants, and anti-inflammatory compounds prior or during pregnancy may have a beneficial effect. However, the safety of such actions should repeatedly be tested to avoid adverse health effects in a developing fetus.

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Hypothesis

We hypothesize that Hg may serve as an additional link between maternal obesity and ASD. In particular, it is supposed that obesity is associated with excessive accumulation of Hg in

the maternal organism. After conception, the fetus is developing in the conditions of Hg overload within the body of obese women thus predisposing to the development of ASD.

Review of evidential support

Obesity epidemiology

Obesity is a metabolic disorder considered to be a worldwide epidemic [1]. It has reached epidemic proportions in developed

* Corresponding author at: Orenburg State Medical University, Sovetskaya St., 6, Orenburg, 460000, Russia.

E-mail address: tinkov.a.a@gmail.com (A.A. Tinkov).

high-income countries [2]. For example, the results of NHANES 2007–2008 indicate a marked increase in obesity rate between the late 1980s and 2000s [3]. However, later studies demonstrated that a significant change did not characterize the prevalence of obesity in the US in 2009–2010 as compared to 2003–2008 [4]. In turn, a marked increase in obesity rate is observed in developing countries [5] where it has tripled over the past 20 years [6]. From 1978 to 2004 the increased rate of obesity was detected not only in adults but also in children and adolescents [7]. Although the incidence of obesity in children did not change from 2009 to 2011 in Canada, it remains a public health problem [7]. Moreover, adolescent obesity increases the risk of severe obesity in adulthood [8]. Females have higher incidence of obesity than males. In particular, a recent study demonstrated that in the 68 tested countries there were three obese women for two obese men [9]. In turn, female obesity is directly related to the incidence of maternal obesity. In particular, the proportion of pregnant women who are obese has doubled since 1989–2007 in the UK having a significant impact on the health of both mothers and infants [10]. It is notable that in parallel with the increased rate of obesity in a general population the rate of weight counseling in patients with obesity and obesity-related pathologies has significantly declined [11].

Autism epidemiology

Autism spectrum disorder (ASD) is a behaviorally defined neurodevelopmental disorder that usually is diagnosed in children during the first 3 years of life [12]. ASD is characterized by pervasive deficits in social interaction, impairment in verbal and non-verbal communication, and stereotyped patterns of interests and activities. Over time, the definitions of autism have changed, and numerous diagnostic criteria have been used in both epidemiological and clinical settings. The previous version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) listed three distinct subgroups for ASD: autistic disorder (AD), Asperger syndrome and pervasive development disorder-not otherwise specified (PDD-NOS) [13]. In 2013, a new edition of this manual was published (DSM-5), which replaced these subgroups with one broad diagnosis of ASD [14]. Autistic individuals are now placed on a continuum depending on the severity of their symptoms. The diagnosis is based on characteristic clinical signs because there so far are no known biological markers [15]. ASD has a multifactorial etiology involving interactions between genetic, environmental, immunological, metabolic and nutritional factors [16–19]. Most of the children with ASD are diagnosed ASD is almost five times more common in boys than in girls [20]. The first survey of autism in 1966 estimated a prevalence of 4 per 10,000 [21]. In 1999, the prevalence of classic autism was estimated to be 10 per 10,000, and for all autism spectrum conditions was estimated at 30–60 cases per 10,000 [22]. These estimates were based on studies from Europe, USA, Canada and Japan. Since then, the number of children with ASD has increased at an alarming rate [23]. The current estimate in the US is that one child in 45 has a diagnosis of ASD [24]. This is notably higher than the previous US government estimate, released in March 2014, of 1 in 68 children with ASD [23]. The UK has had a similar increase in the autism prevalence, and 1.7% of the children in the country is now estimated to have ASD [25]. The increase in the prevalence of ASD since 1979 can only partly be explained due to improvements in diagnosis and greater awareness [26]. Overall, 2–3% of the families have more than one autistic child. Concordances for ASD have been found to be very high in monozygotic twins compared with dizygous twins [27,28].

In recent decades there has been a significant increase in both ASD and obesity. That observation suggests a link of increased rate

of ASD with increased incidence of obesity and associated metabolic disorders like diabetes [29].

Maternal obesity and autism

Obesity is considered to be a negative factor affecting pregnancy outcome and offspring health [30,31]. The presence of maternal overweight and obesity before and during pregnancy is tightly related to cognitive [32] and neuropsychiatric disorders in offspring [33]. Since the 2010s, a growing body of data regarding the association between maternal obesity and ASD has appeared. In particular, in a cohort study of 61,596 women, it has been demonstrated that the values of BMI (>30) at age 18 are significantly associated with increased risk of ASD [34]. A cohort study involving 129,733 children born between 1990 and 2002 in Nova Scotia, Canada demonstrated that maternal pre-pregnancy weight of 90 kg is associated with increased risk of ASD in offspring. At the same time, in children with high genetic susceptibility to ASD maternal obesity as well as other analyzed maternal and obstetric factors played a lesser role [35]. Obese mothers have been shown to have a 67% higher risk of ASD in children as compared to lean ones [36]. A positive association between prepregnancy BMI and the risk of ASD in children was also detected in a study of diabetes-associated ASD risk [37]. The association between maternal obesity and ASD at age 2 was also demonstrated in a cohort of preterm children [38]. At the same time, another study performed in Utah detected a significant association between the risk of ASD and pregnancy weight gain but not prepregnancy BMI [39].

Despite the presence of populational and clinical observations, the exact mechanism of such association is still unclear. Experimental studies demonstrated that high-fat induced maternal obesity results in diminished proliferation and maturation of stem-like cells both in the fetal hypothalamus and neocortex [40] associated with altered gene expression [41] in rats. However, neuroimaging measures of neonatal brain structure in the above mentioned clinical study [38] were not associated with maternal obesity. Altered regulation of 205 genes related to decreased brain apoptosis, lipid, insulin and appetite dysregulation, and furthermore increased estrogen and inflammatory signaling was detected in fetuses of obese pregnant women [42]. Perinatal programming of offspring behavior by high-fat diet may involve modulation of a broad range of signaling pathways [43]. Therefore, the search for the leading factors and potential links linking maternal adiposity and ASD is of particular interest.

Obesity and mercury levels

Recent studies have demonstrated an association between Hg exposure, Hg status, and obesity. In particular, the results of KNHANES IV have shown that blood mercury (BHg) levels are tightly associated ($p < 0.001$) with the incidence of obesity and overweight (BMI > 23) in a fish-consuming population [44]. Later Korean investigations involving 5388 [45] and 9228 [46] persons confirmed this observation. Correlation between BHg and waist circumference ($r = 0.27$, $P < 0.001$) was also detected in Hg-exposed non-diabetic persons living near a deserted pentachlorophenol and chloralkali factory [47]. Moreover, BHg concentration was positively associated with morphometric parameters of obesity even after adjusting for confounders including fish consumption [48]. Also, examination of 477 adults aged 40–65 years living in coastal areas revealed a significant relationship between BHg and waist-to-hip ratio after adjusting for age, sex, alcohol intake, and smoking status [49]. In addition, the previous examination of 719 women and 510 men with a low rate of fish consumption (Orenburg region, continental Russia) demonstrated significantly elevated hair Hg content in overweight and

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