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Perinatal hypothyroidism increases play behaviors in juvenile rats

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ABSTRACT

Thyroid hormones play an instrumental role in the development of the central nervous system. During early development, the fetus is dependent on maternal thyroid hormone production due to the dysfunction of its own thyroid gland. Thus, maternal thyroid dysfunction has been shown to elicit significant abnormalities in neural development, neurochemistry, and behavior in offspring. Previous reports have suggested that human maternal hypothyroidism may increase the chances of having children with autism spectrum disorder and attention-deficit/hyperactivity disorder. However, very few studies have evaluated social behaviors in animal models of perinatal hypothyroidism. To evaluate the possibility that hypothyroidism during development influences the expression one of the most commonly observed non-reproductive social behaviors, juvenile play, we used the validated rat model of perinatal hypothyroidism by methimazole administration (MMI; 0.025% in drinking water) from GD12-PD23. Control animals had regular drinking water. During adolescence (PD33-35), we tested subjects for juvenile play behavior by introducing them to a same-sex, unfamiliar (since weaning) littermate for 30 min. Play behaviors and other behaviors (sleep, social contact, locomotion) were then scored. MMI-treated subjects played more than twice as much as control animals, and the increase in some behaviors was particularly dramatic in males. Locomotor and other affiliative social behaviors were unaffected. These data suggest that perinatal hypothyroidism may alter the organization of the neural networks regulating play behaviors, but not other social behaviors. Moreover, this implicates perinatal hypothyroidism as a potential etiological factor in the development of neurobehavioral disorders, particularly those characterized by heightened social interactions and impulsivity.

1. Introduction

Thyroid hormones (thyroxine, T_4; triiodothyronine, T_3) are critical for the maturation of the fetal central nervous system. Thyroid deprivation during prenatal and neonatal development in animal models significantly impairs neural development in many areas of the brain, including the cortex, hippocampus, and striatum (Bernal, 2005; Porterfield and Hendrich, 1993; Zoeller and Rovet, 2004). Moreover, perinatal hypothyroidism alters the functioning of several neurochemical systems, including dopaminergic, serotoninergic, and GABAergic networks (Ahmed et al., 2010; Rastogi and Singhal, 1974, 1976, 1979; Vaccari et al., 1990). However, although thyroid hormone receptors are densely expressed throughout the fetal brain (Bauer et al., 2002; Chan and Kilby, 2000; Iskaros et al., 2000; Patel et al., 2011), the thyroid gland itself does not become functional until embryonic day 17.5–18 in rats (16–20 gestational weeks in humans) (Morreale de Escobar et al., 2004; Obregon et al., 2007). Until this point, thyroid hormones are derived from the mother through the placenta (Patel et al., 2011). Maternally derived T_4 can be converted to T_3 locally via deiodinase 2 (found in astrocytes) to promote neural outgrowth, elaboration, differentiation, proliferation, and synaptogenesis (Ausó et al., 2004; Moog et al., 2015; Patel et al., 2011; Zoeller and Rovet, 2004).

Some behavioral effects of hypothyroidism on perintal development have been characterized in animal models, but thus far these are largely limited to alterations in locomotor activity, spatial awareness, and cognition (Akaike et al., 1991; Gerges et al., 2004; Goldey et al., 1995; MacNabb et al., 1999, 2000; Tamasy et al., 1986). The most consistent behavioral alterations observed are hyperactivity and augmented locomotor behavior (Akaike et al., 1991; Darbra et al., 1995; Negishi et al., 2005). Other behavioral findings tend to be inconsistent or contradictory, which is likely due to varying experimental protocols. Indeed, the time of onset, duration, and magnitude of thyroid hormone deficiency appears to determine the behavioral outcome on the offspring (Porterfield and Hendrich, 1993). The effects of hypothyroidism throughout the perinatal period on social behaviors have not been explored, despite previous reports attributing this condition in the pathogenesis of neuropsychiatric disorders characterized by alterations in social behaviors, such as autism spectrum disorder and attention-

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deficit/hyperactivity disorder (Andersen et al., 2014; Berbel et al., 2014; Lyall et al., 2017; Negishi et al., 2005; Roman et al., 2013; Sadamatsu et al., 2006).

An appropriate method to evaluate the impacts of perinatal hypothyroidism on social behaviors is to examine juvenile social play behaviors. In most mammals, these interactions are the first non-maternal-guided social behaviors (Trezza et al., 2010; Vanderschuren et al., 1997). Perhaps most importantly, these behaviors serve to teach juveniles how to anticipate the response of a conspecific, which is a key component in the development of a normal, flexible social structure (Bekoff and Allen, 1997; Pellis and Pellis, 2009). Rats reared in isolation, lacking the opportunity to play, show significant impairments in social behaviors throughout adulthood (Byrd and Briner, 1999; Day et al., 1982; Duffy and Hendricks, 1973; Gerall et al., 1967; Hol et al., 1999; Van den Berg et al., 1999a, 1999b). Play behaviors are characterized by rough-and-tumble play fighting interactions (Vanderschuren et al., 1997) that peak in early to mid-adolescence (PD30-40; Ward and Stehm, 1991). The organization of these encounters is based on a solicitation and response system and has previously been described (Pellis and Pellis, 2009; Vanderschuren et al., 1997).

Thus far, only one study has examined the effect of hypothyroidism during development on juvenile rat play. Melancia et al. (2017) found that prenatal hypothyroidism did not affect most play behaviors; the only effect of treatment that they saw was that treated males followed their play partners (an act of solicitation) more than control males. However, because much of the neural development that thyroid hormones orchestrate extends into postnatal development in rodents (Babu et al., 2011; Chantoux and Francon, 2002; Kalaria and Prince, 1986; Rastogi and Singhal, 1974; Vaccari et al., 1990), this does not exclude a role of thyroid hormones in the maturation of play-critical neural circuitry. Furthermore, many of the developmental milestones that occur during late gestation in humans occur during the first few postnatal weeks in rats (Clancy et al., 2007; Pressler and Auvin, 2013; Semple et al., 2013; Workman et al., 2013). Therefore, to gain a better understanding of the complete influences of maternal hypothyroidism in humans, it is necessary to look at hypothyroidism throughout the perinatal period in rats.

The purpose of the current study was to investigate the role of perinatal thyroid hormones on the development of juvenile play behavior. We used an established model of hypothyroidism using methimazole (MMI), which prevents thyroid hormone synthesis by inhibiting the incorporation of iodine into the thyroid hormone precursor thyroglobulin (Amara et al., 2011; Capen and Martin, 1989; Cooper et al., 1984; Ohtaki et al., 1996). We began administering MMI to subjects at GD12 because placental circulation is fully established and both thyroid hormones and thyroid receptors are present in the rat brain at GD11.5–13 (Ahmed, 2015; Barez-Lopez and Guadano-Ferraz, 2017). Our treatments continued until PD23 because, although the exact timing of specific thyroid-dependent developmental events are not known, this range includes the time during which many behaviors and neural networks are organized by thyroid hormones (Ahmed et al., 2010; Henck et al., 1996; Johanson et al., 1980; Rastogi and Singhal, 1974, 1976, 1979; Vaccari et al., 1990; Zoeller and Rovet, 2004).

2. Materials and methods

2.1. Subjects

Timed-pregnant Long-Evans rats were obtained from Envigo Laboratories (Indianapolis, IN) and housed in clear cages (39 × 32 × 19 cm, Lab Products, Inc.) with woodchip bedding (Envigo Teklad Sani-Chips® 7090) and compressed cotton squares for enrichment. Subjects were given rodent chow (Envigo Teklad 7002) and water *ad libitum*. Cages were kept in a continuously filtered ventilation rack (Lab Products, Inc.). Ambient conditions were maintained at 20 ± 1 °C, ~60% humidity, and on an automatically-regulated 12 hour light:12 hour dark photoperiod. Dams were housed individually upon arrival (GD10–11). All of our procedures were approved by Mercer University's Institutional Care and Use Committee and were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Induction of perinatal hypothyroidism

Dams were randomly assigned to a group upon arrival. Beginning at GD12, the treatment dams (n = 6) were administered 0.025% MMI (Sigma) via drinking water. The control dams (n = 7) received regular tap water. After pups were born, each dam and her pups received the same treatment that they had been previously assigned to (either MMI or control water) until PD23. On PD2, the number of pups from each litter was counted, and pups were removed from the home cage briefly to be weighed, and an average pup weight for each litter was calculated. This process was repeated on PD7, 12, 17, and 22. Pups were weaned on PD23 (slightly delayed to ensure that the smaller MMI-treated pups could properly reach water bottles), and at this point all pups were given regular tap water.

The same or very similar MMI administration paradigms have been observed to significantly reduce free T_3 and T_4 in pregnant dams and pups, and increase thyroid stimulating hormone levels up to 10-fold (Ahmed et al., 2010; Barradas et al., 2000; Darbra et al., 2003; Melancia et al., 2017; Özgür et al., 2016). Although we did not measure exact water consumption, dams drank approximately 100–200 ml water per day (this increased across gestation), which exposed them to 0.025–0.05 g MMI/day. Importantly, when pups revert to drinking tap water after weaning, thyroid hormone levels return to control levels (Darbra et al., 1995; MacNabb et al., 1999, 2000; van Wijk et al., 2008).

2.3. Behavioral analysis

Both males and females were used as subjects (control subjects: n = 10 males, 14 females; MMI-treated subjects: n = 10 males, 9 females). At weaning, pups were housed with one same-sex littermate (for a litter of eight pups, they were separated into two cages of two males and two cages of two females). No more than two males and two females per litter were used as subjects. Between PD33 and PD35, subjects were tested for play behavior. One pup in the cage was randomly assigned to be the subject, and the cagemate was removed. Then, a same-sex littermate of the subject that had been housed separately since weaning was marked with a marker and placed into the subject's home cage (the stimulus animal). No isolation period was used prior to behavioral testing in this study. Behavioral interactions were videotaped for 30 min, and all testing was performed between 10:00–12:00. The videos were analyzed by a single observer (SGS). The frequency and duration of each behavior was recorded using Stopwatch + (GSU Center for Behavioral Neuroscience).

The quantified play behaviors have previously been documented (Trezza et al., 2010; Vanderschuren et al., 1997). Play bouts began when the subject or stimulus animal solicited or engaged in any type of play behavior (pins, pounces, wrestling/boxing, following). We defined the end of the play bout when no play behaviors were observed for 3 s. The specific play behaviors (listed above) that the subject initiated were also scored. Pins occurred when the subject animal held (pinned) the stimulus animal down on its dorsum for a few seconds. Pounces were rapid dorsal attacks on the stimulus animal by the subject animal. The duration of pounces was not scored due to its rapid nature. Wrestling/boxing occurred when both animals stood on their hindlimbs and pushed or grabbed their partner with their forelimbs. Following was scored when the subject animal chased the stimulus animal.

The quantified non-play behaviors included social contact and locomotion. Social contact was any non-play social interaction where the stimulus and subject animals were in direct physical contact. This

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