https://doi.org/10.48047/AFJBS.6.7.2024.2968-2982

REVIEW ON HYPOTHYROIDISM AND ITS EFFECT ON VASOPRESSIN AND OXYTOCIN HORMONE via DIO3 RECEPTOR

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Article History

Volume:6,Issue7,2024
Received:30May2024
Accepted:26June2024
doi:10.48047/AFJBS.6.7.
2024. 2968-2982

ABSTRACT

Deiodinases, homodimeric thioredoxin fold-containing selenoproteins, and thyroid hormone signalling are specialised in a time- and cell-specific manner by these proteins. This guarantees sufficient T3 activity in growing tissues, healthy individuals, and a variety of disease situations. By transforming the prohormone T4 into T3, the physiologically active thyroid hormone, D2 activates thyroid hormone. D2 expression is tightly controlled by transcriptional mechanisms that are activated by both endogenous and exogenous stimuli. Moreover, there is a catalytically-activated on/off switch mechanism for D2 activity that works with D2 ubiquitination and deubiquitination. T4 and T3 molecules are both rendered inactive by D3, which stops the thyroid hormone's function.

Deiodinases influence the intracellular levels of T3, which in turn affects gene expression on a cell-specific basis, and so play a role in thyroid hormone homeostasis, development, growth, and metabolic control. With coordinated reciprocal alterations in D2-mediated thyroid hormone activation and D3-mediated thyroid hormone inactivation, tight regulation of these pathways by T3 is frequently attained. Here, we investigated the impact of a local increase in thyroid hormone action in the brain caused by a DIO3 deficit on social behaviours. Dio3 -/- mice of both sexes showed a significant increase in aggression-related behaviours and minor abnormalities in olfactory function, despite the fact that we did not notice changes in friendliness.

In addition, 85% of Dio3 -/- dams showed increased hostility towards the young and no pup retrieval behaviour. Oxytocin (OXT) and arginine vasopressin (AVP), two neuropeptides with crucial functions in shaping social interactions, were found to have sexually dimorphic changes in their physiology that were linked to the maladaptive social behaviours of Dio3 -/- mice. Low levels of OXT and AVP in adult serum as well as aberrant OXT, AVP, and their receptor expression in the neonatal and adult hypothalamus were among these changes. Our findings show that DIO3 is necessary for healthy aggressive and maternal behaviours and suggest that social deficiencies linked to neurodevelopmental disorders may originate from improper local regulation of thyroid hormone action in the brain.

INTRODUCTION

THYROID HORMONE

Iodide is absorbed and concentrated by the thyroid gland where it is used to create thyroid hormones, which are biologically active molecules. Its spatial placement and amount of iodide atoms within the thyroid hormone molecule determine their biological action as well as other intrinsic features. The thyroid gland's primary hormone is thyroxine (T4). It is barely active and has a long half-life of around 8 days. Fully active thyroid hormone T3 (3,5,3'-triiodothyronine) is created primarily outside the thyroid gland through deiodination of T4 and has a substantially shorter half-life (12 h).

Reverse T3 (3,3',5'-triiodothyronine) and T2 (3,3'-T2), on the other hand, are produced when the inner T4 or T3 ring iodine is removed and are biologically inert compounds. Enzymes called deiodinases are responsible for catalysing this activating and inactivating processes. They form biochemical pathways that start or stop thyroid hormone function and are expressed in a variety of organs and

tissues. The deiodinases are involved in a number of physiological processes in vertebrates, including development[1], TSH and TRH feedback regulation[2–4], and disease states[5].

ESSENTIAL FACTORS OF DEIODINASES

Deiodinases of types 1 and 2 (D1 and D2) activate thyroid hormone, but D3 inactivates both T4 and T3 [6-9]. On the other hand, removing the inner T4 or T3 ring iodine results in According to sequence analysis and hydrophobic cluster analysis (HCA), the deiodinases have a 50% overall sequence similarity. The conserved thioredoxin-fold (TRX) domain, which is made up of a and a motifs, is where the most similarity is seen[10]. Deiodinases have a catalytic globular domain that faces the cytoplasm and are anchored in cell membranes by a single transmembrane domain[11, 12]. Mouse D3 globular domain crystallisation helped to further improve this model[13]. The three deiodinases' predicted molecular weights range between 29 and 33 kDa according to their cDNA[14]. Deiodinases are, however, discovered in greater molecular weight complexes in gel filtration investigations, between 44 to 200 kDa[15], indicating that they may be a component of multi-protein complexes.

Deiodinases are homodimers, and catalytic activity requires dimerization[11,16–18]. The trans-membrane and globular domains of the deiodinases are involved in dimerization, which may be mediated by disulfide bonds[17]. The deiodinase active centre is a pocket defined by a motif and a highly conserved intervening region that is also present in the lysosomal enzyme a-L-iduronidase.

The uncommon amino acid selenocysteine (Sec), essential for the nucleophilic attack that occurs during the deiodination reaction[10], is found in this pocket. Thyroid hormones must conform to the topology of all three deiodinases in order to enter cells where they are processed by deiodinases. Membrane transport proteins mediate cell entrance[19], with monocarboxylate 8 (MCT8) probably being the most important one.

Neurodevelopmental issues and endocrine dysfunctions are linked to mutations in the MCT8 gene[19,21]. The biological effects of thyroid hormone are started when T3 binds to two nuclear thyroid hormone receptors (TRs), TRa and. TRa and affect transcription of several sets of thyroid hormone-responsive genes. It is also known that D2 and D3 have antagonist roles in thyroid hormone activity by inversely altering intracellular T3 levels since TR saturation depends on the quantity of intracellular T3. Thyroid hormone signalling is increased by D2 producing T3, whereas it is silenced by D3 inactivating T4 and T3. Both routes are mostly unaffected by amounts of T4 or T3 in the blood[22,23].

The coordinated expression of D2 and D3 is a corollary of such investigations, which demonstrates that thyroid hormone action can be tailored in a time- and cell-dependent manner[1,24]. Vertebrate development is a well-known example of this interaction. D3 activity predominates in the majority of growing tissue, shielding quickly developing cells from thyroid hormone exposure. D2 expression rises and D3 expression decreases as the embryo ages, improving thyroid hormone signalling. D1, however, makes only a little contribution to the local regulation of thyroid hormone signalling. This is explained by its location in the plasma membrane, which allows for the quick release of T3 produced by D1 back into circulation. In fact, D1 contributes less to the maintenance of circulating T3 in humans than it does in rats, where it accounts for around half of the daily extrathyroidal synthesis of T3[28,36].

Furthermore, research using D1 knockout (KO) mice suggests that D1 also serves as a scavenger, preferring deiodinating sulfated forms of iodothyronines when they are excreted in the urine and bile[27,37-40].

SOCIAL BEHAVIOUR AND THYROID HORMONE

While thyroid hormones and their influence on mood disorders have received attention in recent years, little is known about their role in social behaviours such as friendliness, aggression, and parental conduct[28]. Oxytocin (OXT) and arginine vasopressin (AVP), two important regulators of social behaviour, have been thoroughly investigated in many animal models[41-49] Therefore it's likely that social behaviours are influenced by changes in the factors that determine how brain thyroid hormones work. Here, they discovered that increased aggressive behaviours in mice of both sexes and clearly impaired maternal behaviour in females are caused by the excess brain thyroid hormone that develops in DIO3-deficiency.[50-52]

These aberrant phenotypes occur at the same time as changes to the OXT and AVP systems' physiology. Their findings show that the social abnormalities connected to neurodevelopmental disorders in humans may be caused by DIO3 modulation of brain T3 activity. The purpose of our study was to analyse and evaluate previous studies to determine how the hormones vasopressin and oxytocin affect a person's social behaviour as a result of altered secretions of T3, T4, and TSH hormones acting on the DIO-3 receptor as a result of hypothyroidism.

DISCUSSION

Increased aggression and hostility in D3-deficient mice Then, when faced with an intruder in their home cage, we looked into the aggression-related actions of DIO3-deficient mice of both sexes.

Dio3+/+ female residents spent more than half the time pursuing the invader through the cage after it was put there. This movement was often accompanied by sniffing. This period was significantly reduced in the Dio3-/- females (Fig. 1) (F(1, 44)=49.35, P0.001). Although the Dio3+/+ men spent substantially less time pursuing the intrusion, this behaviour was obviously sexually dimorphic. In Dio3-/- males, this time dropped even more, but the difference was not significant (Fig.1).

Overall, female Dio3+/+ mice and Dio3-/- mice engaged in social investigation for about the same amount of time (nose, anogenital and body sniffing). Dio3+/+ males investigated the invader for more than twice as long as the females did. Nevertheless, in Dio3-/- males, this period was shortened by 65% (F(1, 44)=23.28, P0.001; Fig. 1). We found that male Dio3-/- explored the intruder less frequently than Dio3+/+ males, despite the fact that female Dio3-/- did. Male Dio3-/- subjects had half as many social investigation approaches as Dio3+/+ subjects (F(1, 44)=67.51, P 0.001; Fig. 1). All of the Dio3-/- animals of both sexes displayed some form of threat behaviour, but only 54% of the female and 67% of the male wild type mice tested displayed any type of threat behaviour (females: F(1, 23)=6.24; males: F(1, 25)=5.16; Fig. 1).

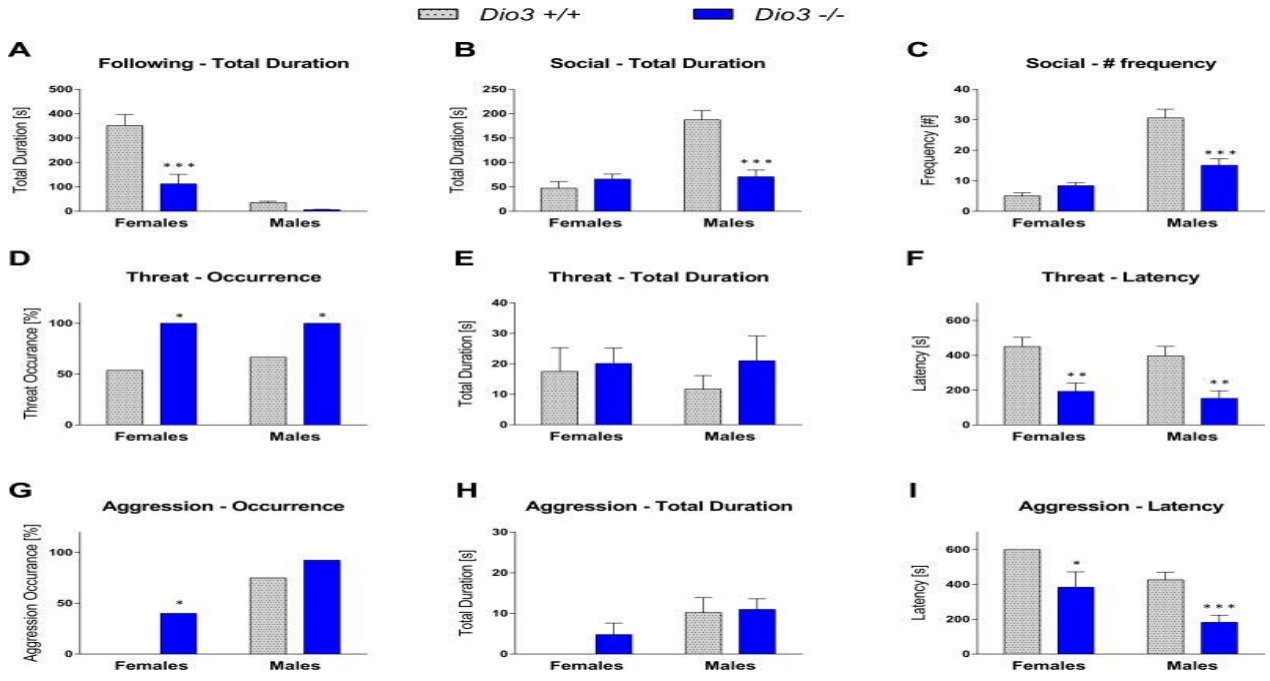

Fig. 1-Threat and aggressive behavior in Dio3−/− *mice. Total durations of social exploration (A), following the intruder (C), threat (E) and aggressive behavior as well as social frequency data (B), occurrence of threat (D) and aggressive (G) behavior and their latencies (F&I) were measured in resident-intruder tests.* Dio3+/+ *and* Dio3−/− *animals served as residents and the intruder mice were age, size and gender matched. Scored threat behavior includes tail rattling, thrust, lateral threat, mounting, crawling under and pushing past the intruder. Data are shown as mean ± SEM with n = 10–13 mice per experimental group.*[54]

When compared to Dio3+/+ men, the overall length of threat behaviour was identical in Dio3-/- males, but trended greater in Dio3+/+ males (Fig.1). Both male and female Dio3-/- mice showed significantly reduced threat behaviour latency than Dio3+/+ mice (F(1, 44)=24.48, P0.001; Fig. 1). Threatening behaviour did not necessarily develop into combative, boxing, upright, pinning, biting, or assaulting behaviour. None of the Dio3+/+ females exceeded the 40% of Dio3 -/- females who exhibited aggressive behaviour (F(1, 23)=6.29, P 0.05; Figure 1).

The majority of males in both genotypes exhibited aggressive behaviour, with Dio3-/- mice showing this behaviour more frequently (Fig.1). The total amount of time that the aggressive behaviour lasted in Dio3+/+ and Dio3-/- males was comparable to that seen in Dio3-/- females and did not differ substantially (Fig.1). Male Dio3-/- mice had a significantly shorter latency to exhibit aggressive behaviours than Dio3+/+ mice (Fig. 1) (F(1, 44)=22.57, P0.001). In contrast to Dio3+/+ females, who exhibited no aggressive behaviour throughout the duration of the test, the latency for aggressive behaviour was also much lower in Dio3-/- females.

It's interesting to note that the delay for aggressive behaviour was similar in Dio3-/- females and Dio3+/+ males (Fig.1). These findings point to a propensity for as well as an increase in aggressive and threatening behaviours in DIO3-deficient mice. / Threat and aggressive behaviour in Dio3-/- mice, Fig. 1. Inhabitant-intruder tests were used to quantify the total lengths of social exploration (A), following the intruder (C), threat (E), and aggressive behaviour, as well as social frequency data (B), occurrence of threat (D), and aggressive (G), and their latencies (F&I). Residents included Dio3+/+ and Dio3-/- animals, and the invader mice were matched for size, gender, and age. Tail rattling, thrusting, lateral threat, mounting, burrowing beneath, and pushing past the intruder are all considered scored threat behaviours.

Each experimental group's n = 10–13 mice data is presented as the mean SEM. 54 According to the papers that were chosen for analysis, aberrant thyroid hormone production starting at the neonatal stage results in an underdeveloped DIO-3 receptor. This causes variations in the hormones vasopressin and oxytocin, which are largely responsible for human social behaviour. Studies revealed that female animals also had lower maternal character levels. These investigations also indicated that newborns exhibited gene-dependent traits that implied the irregularity from birth. / Physiology of oxytocin and vasopressin in adult Dio3-/- mice. OXT and AVP levels in the blood (A & B). Oxt, Avp, Oxtr, and Avpr1a's hypothalamic expression in adults (C F) and dams (G J). At the age of three months, serum and tissue samples were taken. Data are presented as the mean SEM (n = 7 to 10)[52-54]

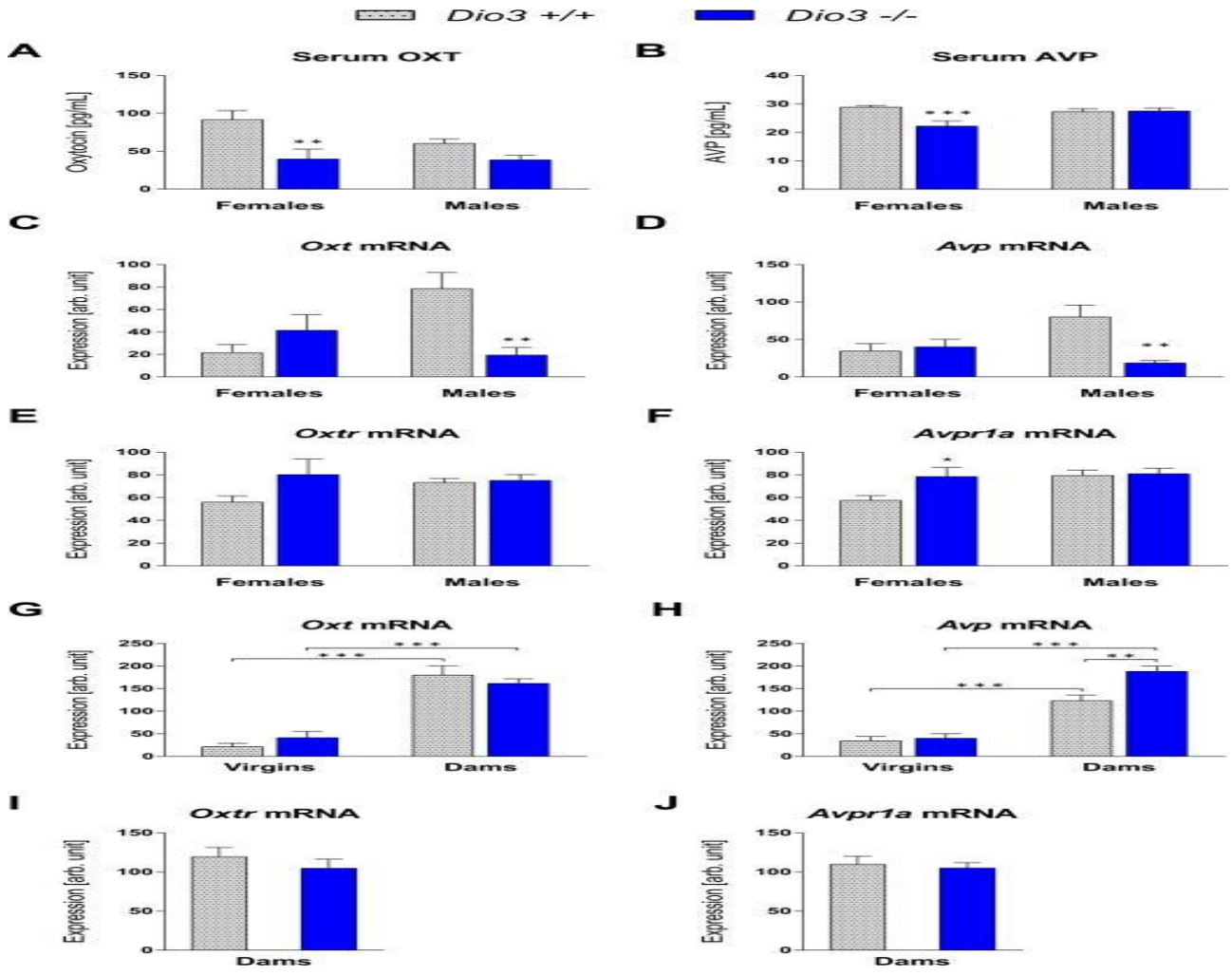

Fig-2 Oxytocin and vasopressin physiology in adult *Dio3*−/− mice. Serum levels of OXT and AVP (A & B). Hypothalamic expression of *Oxt*, *Avp*, *Oxtr* and *Avpr1a* in adults (C–F) and in dams (G–J). Serum and tissue were collected at three months of age. Data are shown as mean ± SEM with n = 7 to 10 (A&B) or 5 to 7 (C–J) mice per experimental group.[54]

Although the research were restricted to animal clinical trials, it is possible that the same outcome would also occur in human investigations. Thyroid hormone levels in the blood. T4 and T3 serum levels in adult mice (A & B). Blood levels in dams of T and T3 (C&D). With n = 6 to 8 (A&B) mice per experimental group, the data are presented as the mean SEM. 54.

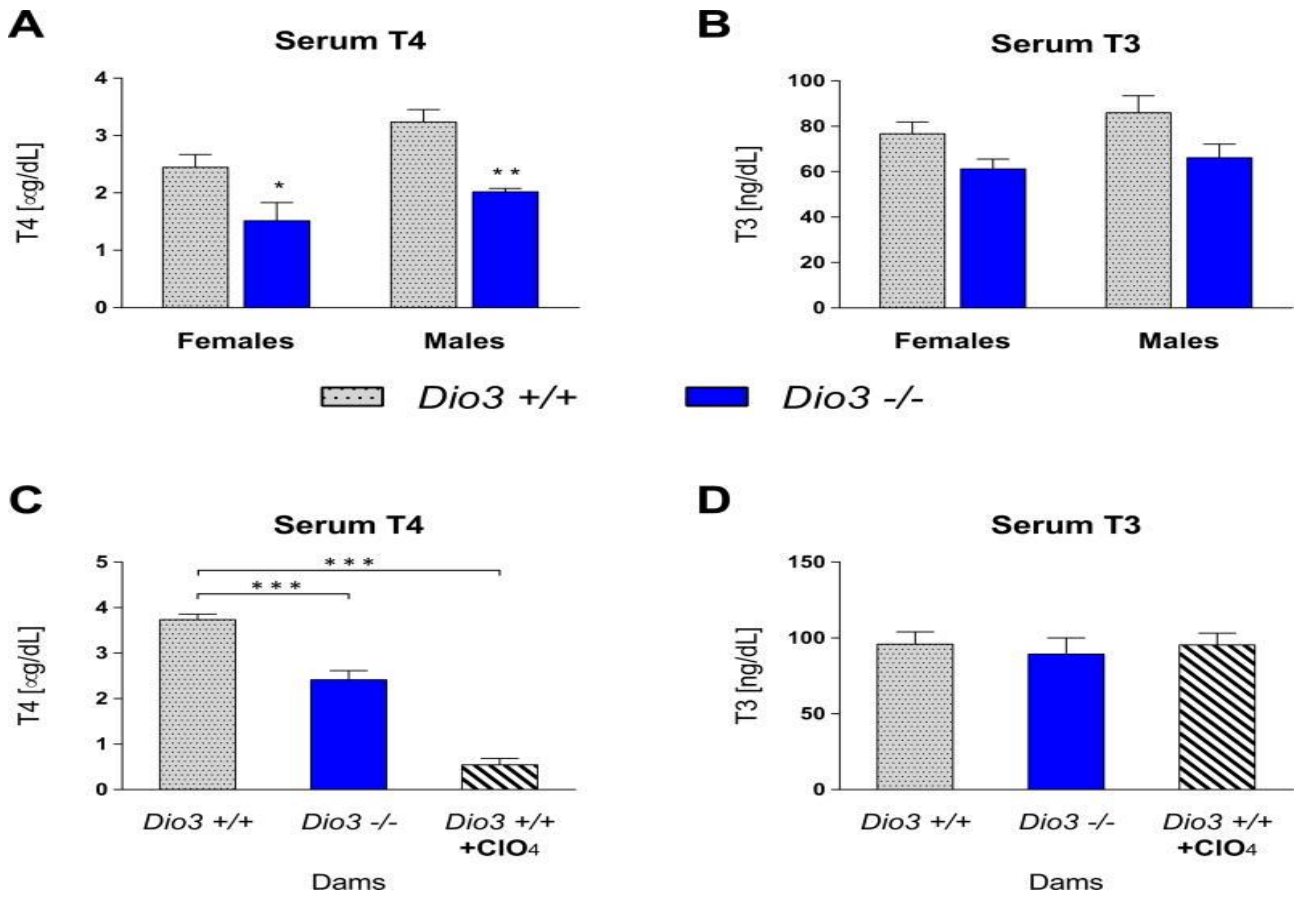

Fig- 3 Serum thyroid hormone levels. Serum levels of T4 and T3 adult mice (A & B). Serum levels of T and T3 in dams (C&D). Data are shown as mean ± SEM with n = 6 to 8 (A&B) mice per experimental group.[54]

Total durations of social disquisition(A), following the meddler(C), trouble(E)and aggressive geste as well as social frequence data(B), circumstance of trouble(D) and aggressive(G) geste and their dormancies(F&I) were measured in occupant- meddler tests. Dio3 and Dio3 −/− creatures served as residers and the meddler mice were age, size and gender matched. Scored trouble geste includes tail rattling,thrust, side trouble, mounting, crawling u nder and pushing past the meddler. Data are shown as mean ± SEM with n = 10 – 13 mice per experimental group.54 The studies taken for review led to the conclusion that abnormality in thyroid hormones since neonatal stage results in unpresentative DIO- 3 receptor. This leads to variation in vasopresssin and oxytocin situations which predominates the social geste in humans. The studies refocused out the dropped situations in motherly character in ladies creaturestoo.Further these studies revealed that babes showed gene dependent characters inferencing the irregularity since birth.

Neonatal Expression Of OXT and AVP

We also looked at the effects of DIO3 deficiency on Oxt and Avp hypothalamic expression at postnatal day 5 (P5), when Dio3/ mice experience both brain and systemic thyrotoxicosis, in light of the possibility that gender-specific abnormalities in neuropeptide systems result from abnormal OXT exposure during development (Yamamoto et al. 2004, 2004). (Hernandez et al. 2006). We discovered that Oxt and Avp expression was significantly higher in Dio3/ male newborns [(F1,29) = 21.67, P 0.001, and (F1,29) = 18.18, P 0.001, respectively for Oxt and Avp], whereas the increase in Dio3/ female neonates was less pronounced and did not achieve statistical significance (Fig. 6a,b). The expression of hairless (Hr), a well-known T3-dependent gene, was similarly and strongly enhanced (Fig. 6c) in Dio3/ mice of the present study, supporting earlier findings (Hernandez et al. 2006).[52-54]

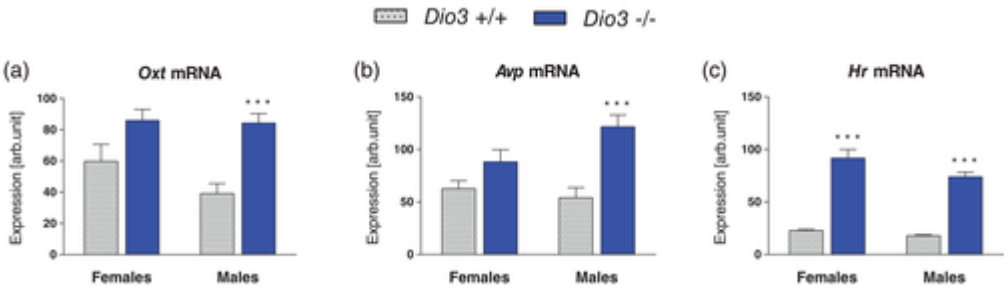

*Figure 4-**Expression of oxytocin and vasopressin in neonatal Dio3−/− mice.** Hypothalamic expression of Oxt and Avp and the T3-dependent gene Hr (hairless) (a-c). Tissue was collected from 5-day old mice. Data are shown as mean ± SEM with n = 6 to 10 mice per experimental group.[54]*

CONCLUSION

The review concluded that the hypothyroidism convinced altered T3, T4, TSH hormones causes imbalanced hormonal concealment of oxytocin and vasopressin, performing in high possibility of having increased social behavioural traits like aggression, dominance, violent studies etc. This can be explained by the action of DIO- 3 receptors on vasopressin and oxytocin hormones in brain. Studies related to this content should be explored to gain further knowledge about mortal brain and its behavioural, neurocognitive patterns. The findings show that loss of DIO3 function causes atypical social behaviours, which may be partly due to contemporaneous changes in neuropeptide physiology. Further research is required to ascertain whether these anomalies are the result of developmental abnormalities and to pinpoint the central nervous system parts that are responsible for these abnormalities. Our findings suggest that illnesses with social deficiencies, such as ASD, schizophrenia, and depression, may be caused by increased

thyroid hormone action in the central nervous system during development or in adulthood. Further research highlights the possible significance of thyroid hormone status of the brain rather than circulating thyroid hormone levels when assessing psychiatric illnesses.

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