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The Role of the Androgen Receptor in Oxytocin Gene Expression: Implications for Mood Disorders

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Abstract

Oxytocin (OXT), which is synthesised in the hypothalamic paraventricular nucleus (PVN) and then released into various brain areas, may play an important role in a variety of behaviours and neuropsychiatric disorders, including depression. Clinical studies have suggested that testosterone has the opposite effect on these disorders as oxytocin. We began by looking at the expression of OXT in the PVN of fifteen patients with mood disorders and fifteen matched controls using immunocytochemistry (ICC) and the co-localization of OXT and androgen receptor (AR) using double labelling ICC in the post-mortem hypothalamus of fifteen patients with mood disorders and fifteen matched controls. Following that, the in vitro regulatory effect of AR on OXT gene expression was investigated. Scientist discovered that mood disorder patients had higher levels of PVN OXT expression than control subjects, and we saw a clear co-localization of AR in OXT-expressing neurons, both in the cytoplasm and in the nucleus. Furthermore, after pre-incubating the SK-N-SH cells with testosterone, OXT-mRNA levels were found to be significantly lower. Electrophoretic mobility shift assays and co-transfections in neuroblastoma cells revealed another potential androgen-responsive element in the human OXT gene promotor. Finally, in vitro studies revealed that AR mediated the suppression of OXT gene expression. These findings suggest that the fact that OXT and testosterone appear to have opposing effects in neuropsychiatric disorders may be due to a direct inhibition of AR on OXT transcription, which may provide a novel target for therapeutic strategies in depression.

Keyword: Gene expression • Mood disorder • Oxytocin • Androgen receptor

Introduction

The neuropeptide oxytocin (OXT) is produced in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON). When released from the neurohypophysis, it may act as a neurohormone, influencing uterine contractions and milk ejection during parturition and lactation. PVN OXT, which is synaptically released into different brain areas and plays a central role as a neuromodulator, has received increased attention in recent decades. OXT's central effects include affective social behaviours such as maternal care and pair bonding, attenuation of fear and the stress response, and modulation of symptoms of psychiatric disorders such as major depressive disorder (MDD) and bipolar disorder (BD). Intranasal OXT administration has been used to study the social and/or clinical effects of OXT. However, the belief that all of the effects of intranasal OXT can be explained by direct OXT action on brain systems has been called into question. Furthermore, the literature is ambiguous on the direction of OXT changes in depression. Serum OXT levels, for example, have been found to be both increased and decreased in mood disorders (Ozsoy et al, 2009). Because of these considerations, postmortem brain research on the OXT system in clinically and neuropathologically well-characterized patients with mood disorders is critical. Although we had previously observed an increase in the number of OXT-expressing neurons in the hypothalamic PVN in depression in a relatively small study, we needed to confirm this finding in a larger and independent brain sample, and we also needed to figure out how testosterone regulates OXT expression.

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Literature Review

A number of studies have indicated that the steroid receptor family is involved in the control of the activity of stress-related neuropeptide neurons in the hypothalamic PVN, which may be a key step in the pathophysiology of mood disorders. However, despite a study by Zhou et al. showing that OXT-expressing neurons in a specific area of the rat PVN, namely the ventral zone of the medial parvocellular region of the PVN, co-express androgen receptor (AR), and a different study stated that rat PVN lacked AR. Scientist also discovered distinct AR expression in the human PVN. Recent theories have suggested that OXT and testosterone have conflicting effects on cognitive and behavioural processes as well as on a number of neuropsychiatric disorders, including autism, schizophrenia, and depression [1]. This raises the intriguing possibility that androgens play a role in the regulation of OXT expression in humans. Therefore, in the current work, we first looked at the PVN OXT expression in depression and any potential AR co-localization in OXT-immunoreactive neurons in the PVN in postmortem human brain tissue. We investigated the regulation of testosterone on OXT gene expression via AR as a nuclear transcriptional factor after we were able to confirm, in the largest sample to date, the presence of a greater amount of PVN OXT expression in depression patients and observed a clear co-localization of nuclear AR in OXT-immunoreactive neurons [2]. We subsequently observed an inhibiting effect of AR on human OXT gene expression. The data from our largest collection of postmortem material to date demonstrate that patients with mood disorders have higher levels of PVN OXT expression, while a new discovery is the co-localization of AR in some of the human PVN OXT-immunoreactive neurons. The co-localization of AR in the cytoplasm and nucleus of human PVN OXT neurons suggests that androgens may have a direct regulatory effect on PVN OXT gene expression. OXT may impact depressive symptoms in a variety of ways. OXT is a satiety hormone, thus the elevated levels of OXT in the hypothalamus that we saw may be connected to the eating disorders that frequently accompany sadness. On the other hand, OXT has typically been linked to improved pro-social behaviour, and it has been discovered that taking OXT helps to lessen the signs and symptoms of anxiety and sadness [3]. Our observations of greater PVN OXT-immunoreactivity and higher peripheral OXT levels in chronically depressed people initially appear perplexing. Higher OXT expression in depression, however, has been hypothesised to have a

compensatory function by easing anxiety and depressive symptoms. In fact, CRH and OXT have opposite effects: CRH induces the release of cortisol and adrenocorticotropic hormone, whereas OXT prevents corticotropic activity in humans. In contrast, OXT may heighten the awareness of social stimuli, whether they are uplifting or depressing. In this manner, OXT may be linked to increased sensitivity and susceptibility to damaged social relationships, depressive symptoms, and suicidal ideation, depending on polymorphisms connected to the OXT receptor [4]. It was discovered that estrogens, through ER, up-regulate the expression of the human OXT gene. Additionally, the androgen metabolite 5-androstane-3,17-diol (3-diol), when combined with a hormone-responsive region in the rat OXT gene promoter, was discovered to have the ability to up-regulate OXT expression via ER. This is why we conducted our studies using the ER antagonist ICI 182 780 [5]. We have recently seen for the first time that testosterone-induced decreased OXT-mRNA expression in the neuroblastoma cell line SK-N-SH, which possessed endogenous ER, AR, and OXT expression. It is crucial to remember that there are various other variables, such as multiple neurotransmitters and ER, involved in the regulation of OXT expression, therefore changes (whether larger or smaller) in AR expression do not necessarily have an a priori correlate to the changes in OXT in mood disorders [6]. But in addition to our molecular research, which shows a direct regulatory role for AR on OXT gene expression, the theory that AR might contribute to the increased OXT-immunoreactivity in mood disorders is also supported by the lower testosterone levels seen in older sad males and females. Medication is a natural possible confounding factor in any postmortem study. However, we do not believe that antidepressants are a significant factor in our major findings. Previous research has demonstrated that the plasma concentration of OXT did not significantly alter when patients with depression were treated with SSRIs, electroconvulsive therapy, or SSRIs for obsessive-compulsive disorder (Humble et al, 2013). Additionally, it was discovered that haloperidol did not affect rat OXT release when it was administered to one patient with a mood disorder and three controls in the current investigation. Furthermore, despite the fact that Lithium and Valproate have been shown to increase OXT release in rats and OXT mRNA expression in the PVN and SON of the hypothalamus in rats, the mood disorder patients who received these medications had IODs of OXT-immunoreactivity that fell completely within the range of the other mood disorder patients. In addition, it has been demonstrated that benzodiazepines like chlordiazepoxide can prevent the release of OXT in response to unpleasant stimuli, and chronic morphine intoxication in rats can prevent the production of OXT [7]. In our investigation, diazepam was administered to more mood disorder patients (n=9) than control individuals (n=3), while morphine was administered to more mood disorder patients (n=9) than control subjects (n=3). The elevated OXT-immunoreactivity levels seen in patients with mood disorders would have been underestimated if these substances had interfered with our assays.

Discussion

In the human OXT promoter, we later discovered a particular ARE site that might, in theory, be situated either upstream or downstream of the transcription start site of androgen responsive genes. By using EMSA, we confirmed that this ARE (site A) does, in fact, bind to AR nuclear extracts, as shown by two distinct bands, which is in line with a prior report of two AR isoforms. Following co-transfection with an AR-expression plasmid and testosterone therapy, the transcriptional activity of the human OXT promoter significantly decreased, providing evidence that testosterone may inhibit OXT expression. Evidence from a prior study shows that AR and ER interact clearly, maybe in a competitive or antagonistic manner. It's interesting to note that, in line with our current findings, OXT receptor (OXTR) expression was higher in the hypothalamus of AR knock-out mice compared to controls. Together, these results suggest that testosterone may affect oxytocinergic function in a way that is additive. But it should be emphasised that there is also evidence showing that androgens have no effect on OXTR expression. Future research is required to clarify whether OXTR could be used as a new potential target for androgen effects.

Conclusion

Mood disorders are associated with increased expression of the hypothalamic PVN OXT gene and localization of AR in human OXT neurons. According to our findings, the opposing effects of OXT and testosterone on psychological processes and neuropsychiatric illnesses as suggested in the literature may be caused by the AR's direct inhibitory influence on OXT transcription.

Acknowledgement

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Conflict of interest

None.

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