Neuroscience: Epigenetics and the "social" gene

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The discovery that a neuropeptide gene has an association in regulating human social behavior through epigenetic modification provides insight to the biological mechanisms behind human sociability. These findings may provide potential therapeutic targets for psychiatric disorders such as Autism Spectrum Disorder or Schizophrenia.

Evolution of the human species has led to the development of an impressively complex cognitive system that allows for intimate and meaningful sociability1. By having this social-cognitive functionality, humans have been able to exhibit a diverse array of behaviors that can be differentiated from other animal species2. However, it has been a key objective to find the genetic and biological basis that underlies human's social-cognitive capabilities. Oxytocin is a peptide hormone that is created in the hypothalamus, and it may be the answer that connects the dots between the human brain and behavior. Oxytocin has been linked to social behaviors such as trust3, generosity4, learning and empathy5, and nurturing during parenthood6. Evidence on the connection between oxytocin and social behavior has driven research to focus on the genes responsible for the oxytocin system. The gene responsible for the expression of neuropeptide oxytocin is OXT7, and Haas and colleagues8 report that epigenetic modification of the OXT gene is linked to several different measures of sociability in humans.

The OXT gene has been a focus in knockout studies involving social behavior, where the gene is essentially inactivated or disrupted by an artificial piece of DNA. Studies involving rodents have shown that OXT knockout mice (OXT -/-) displayed social learning and memory deficits9 as well as overall aberrations in social behaviors10. Also, polymorphisms of OXT in humans have been linked to psychiatric disorders, such as Autism Spectrum Disorder (ASD)11 and Schizophrenia12. Although OXT is an important contributor to the oxytocin pathway, epigenetic modification of OXT and its influence on the brain and social behavior is currently unknown. Epigenetic modification involves the addition of changes to the DNA sequence, which in most cases temporarily activates or deactivates genes. One factor that affects the expression of genes is DNA methylation. DNA methylation occurs when a methyl group (CH_3) is attached to a promoter region of a target gene responsible for its expression. This "methylation" creates an area on the promoter region called a CpG site, which temporarily turns off gene expression when methylated. Studies have show that an increase in DNA methylation is linked to a decrease in expression of a target gene13.

Therefore, Haas and colleagues tested the hypothesis that reduced DNA methylation of OXT, which would lead to higher OXT expression, influences a greater amount of overt measures of human sociability. Haas et al. collected genetic, behavioral, functional and structural data from healthy patients and analyzed DNA methylation across the promoter region of OXT.

First, the authors looked at individual differences in behavioral measures, such as the anxious/avoidant attachment styles test and the emotional recognition accuracy task by self-report data. These measures were compared to the level of DNA methylation. DNA samples were obtained from saliva. With the attachment style self-report data, higher scores indicated that participants characterized themselves as exhibiting more of a need for reassurance, fear of rejection, as well as the tendency to avoid intimacy, and overall insecure attachment to others. On the other hand, lower scores indicated secure attachment with others. With the emotional recognition accuracy self-report data, participants watched a compilation of clips where emotional facial expressions were presented, and they had to identify the type of emotion that was being elicited.

Haas et al. found that increased OXT DNA methylation was associated with higher anxious/avoidant attachment style scores, indicating that individuals who showed greater DNA methylation of OXT reported that they felt more insecure attachment to others. Also, they found that increased OXT DNA methylation was associated with lower emotion recognition accuracy scores, meaning that individuals with greater DNA methylation of OXT had more difficulty recognizing emotional facial expressions. Analysis of behavioral self-report data gives evidence to the OXT gene having an influence on social behaviors.

Second, the authors collected functional magnetic resonance imaging (fMRI) data while participants underwent two social cognitive tasks designed to elicit neural activity within the mentalizing/empathy network, which responds to oxytocin. The first task was the emotional perspective-taking task, where participants were instructed to connect an emotional expression to the correct social scene. The second task was the emotion attribution task, where participants were shown a picture of a person's face with a targeted emotion as well as a few social scenes and were instructed to decide which social scene caused the person's emotion.

Haas et al. found that, for the emotional perspective-taking task, increased OXT DNA methylation was associated with reduced neural activity in the right superior temporal sulcus (STS), which is a brain region responsible for social perception and processing. Also, for the emotion attribution task, increased OXT DNA methylation was associated with reduced right STS, right fusiform gyrus (Fus), middle occipital gyrus, right inferior frontal gyrus, and left fusiform activity. This meant that individuals with greater OXT DNA methylation displayed reduced neural activity when attempting to understand an emotional perspective and attributing an emotional expression to a specific social scene (Fig. 1).

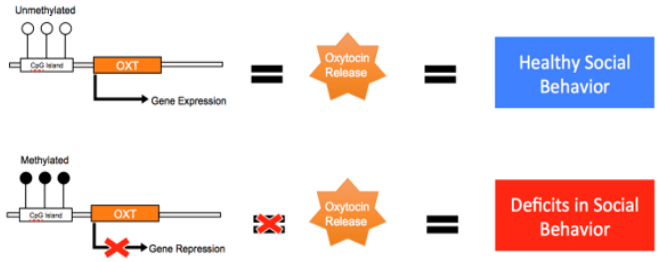

Figure 1: DNA methylation of OXT and social behavior
Haas et al.8 report that DNA methylation of the OXT gene deactivates gene expression, which disrupts oxytocin release and is associated with deficits in different social behaviors.

Finally, the authors collected structural MRI data in order to observe individual differences in regional gray matter volume in association with DNA methylation of OXT. Haas et al. found that increased OXT DNA methylation was associated with reduced gray matter within the right fusiform gyrus. Together, analysis of both functional and structural neuroimaging data gives evidence to the OXT gene having an influence on brain activity that translates to social behaviors.

Haas and colleagues' research identifies the OXT gene as an important link to human sociability. These findings support their hypothesis that epigenetic modification of OXT is associated with individual differences in human sociability; specifically, greater DNA methylation of OXT was associated with anxious/avoidant attachment styles, as well as reduced neural activity and gray matter volume in brain areas responsible for social behaviors and social-emotional perspectives. From these findings, OXT could be a useful therapeutic target for social disorders, such as ASD and Schizophrenia. It would be interesting to test and see if oxytocin medications provide any benefits to social deficits seen in patients.

Although the authors' hypothesis was supported, their findings do not provide direct empirical evidence connecting OXT and human social behavior, specifically in regards to the production, function, and accessibility of oxytocin in the brain. It would be interesting to look at specific molecular modulators in the oxytocin pathway, such as the glycoprotein CD38, and understand the role it plays in leading to human sociability. Also, OXT is not the only gene in the oxytocin pathway. OXTR is the gene responsible for the expression of oxytocin receptors. It would be beneficial to look into the modification of the gene and investigate the specific role it plays in the oxytocin pathway and human social behavior. Overall, this study helps to advance understanding of the genetic and molecular basis of human sociability.

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