SCIENCE REPORT

The Role of Oxytocin in Impaired Social Cognition in Autism Spectrum Disorders

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Autism spectrum disorder (ASD) is an umbrella term that encompasses the diagnoses of Aspberger's disorder and pervasive developmental disorder-not otherwise specified, in addition to the more severe diagnosis of autism. Interest in the causes and treatment of ASD has spiked in recent years due to an increase in prevalence in ASD in children over the last decade, to approximately 3.4 per 1000 children.[1]

Although the causes of ASD are not yet fully understood, a controversial hypothesis that measles-mumps-rubella (MMR) vaccine and thimerosal-containing vaccines cause autism was definitively ruled out by a 2004 Immunization Safety Review.[2] There is much stronger scientific evidence implicating a role of genetics in the development of the disorder; one study determined the heritability of autistic disorders to be around 90%.[3] Genome-wide searches for loci that convey risk for ASD have produced candidate genes on nearly every chromosome,[4] though the genetic basis of ASD remains ambiguous and elusive.[5]

One of the most debilitating impairments that ASD patients must cope with is the development of abnormal social cognition. Research conducted in animals suggests that the uniquely mammalian hormone and neuropeptide oxytocin plays a key role in the development of normal social cognition and behavior in a multitude of species. The aim of this review is to examine studies conducted in nonhuman mammals, as well as recent genomic studies and clinical trials to investigate whether an abnormal oxytocin system may contribute to the development of impaired social cognition in ASD.

Oxytocin injections into the left lateral ventricle of female rats have been shown to cause the full expression of maternal behavior.[6] The onset of normal maternal behaviors in female rats following pregnancy was blocked when oxytocin receptor antagonists were infused.[7] One research team found that patterns of oxytocin receptor density in several brain areas of prairie voles predicted maternal behavior[8] and that blocking these receptors with oxytocin antagonists eliminated spontaneous maternal behavior. Interestingly, one study reported that maternal behavior in rats was highly heritable across generations, but was not attributable to differences in genotype.[9] A subsequent study found that these differences in maternal behavior were associated with differences in oxytocin receptor expression in the central nucleus of the amygdala,[10] a structure thought to be heavily involved in processing emotional content. Studies of postpartum human mothers found that oxytocin levels were correlated with a mental component of human bonding, including attachment-related thoughts and frequent checking of the child.[11]

Other studies found that infant oxytocin receptor knockout mice showed deficits in social discrimination,[12] as did infant oxytocin knockout mice.[13] Infusion of oxytocin in adult male rats was found to double the time spent in physical contact with females.[14] Brain infusions of oxytocin were found to initiate the formation of pair bonds in prairie voles, whereas oxytocin antagonists administered at the same time eliminated the formation of pair bonding.[15] A recently published study found that female prairie voles treated with nucleus acumbens infusions of adeno-associated viral vectors containing gene coding the oxytocin receptor resulted in a local increase in receptor expression and also accelerated the development of partner preferences.[16] Studies in primates have shown that highly social bonnet macaques have high oxytocin levels, whereas socially withdrawn pigtail macaques show lower levels.[17] In humans, double blind administration of intranasal oxytocin prevented subjects from reducing trust of others in the face of betrayal.[18] Additionally, participants who received oxytocin showed reduced brain activity measured by functional magnetic resonance imaging (fMRI) in the amygdala.[18]

Oxytocin administration has also been shown to facilitate social memory and recognition among rats.[19] Male oxytocin knockout mice were found to exhibit symptoms of social amnesia, but social memory was completely restored after brain infusion of oxytocin.[20] Intranasal administration of oxytocin also improved humans' recognition of previously presented faces.[21]

Another study found that intranasal administration of oxytocin was effective in reducing the number and severity of repetitive behaviors over a four hour period in human patients diagnosed with ASD.[22] Recent studies have found that oxytocin administered intranasally was effective in improving the processing of emotional cues conveyed by faces[23] and of emotional content of speech[24] in patients diagnosed with ASD.

Three separate studies examining differences in single-locus alleles and haplotype frequencies between patients with ASD and healthy controls have found single nucleotide polymorphisms (SNPs) and haplotypes conveying heightened risk for autism within the 3p25 region, containing the gene for the oxytocin receptor.[25, 26, 27] One remarkable study found evidence of an epigenetic inheritance due to significant increases in methylation within the promoter region of the gene coding for the oxytocin receptor in ASD patients compared to healthy controls.[28] This hypermethylation was correlated with decreases in oxytocin receptor expression.[28]

These studies suggest that the oxytocin system is heavily involved in the expression of normal social behaviors, including maternal behavior, pair bonding, and social memory

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across several species of mammals. The findings from animal studies have received support from research done in humans linking oxytocin levels to socially relevant variables, such as attachment-related thoughts and trusting behavior.

The oxytocin system likely mediates social cognition via the brain's reward and pleasure system, as increasing the expression of oxytocin receptors in the nucleus acumbens, an area heavily involved in addiction and rewarding behaviors, facilitated pair bonding. The amygdala is also a likely locus of oxytocinergic influence, as it has been linked to social cognition in both in animal and human studies. In humans, the influence of oxytocin on the amygdala may be the basis for emotional processing of socially relevant stimuli.

The findings that intranasal oxytocin administration alleviated deficits in emotional processing as well as repetitive behaviors, two of the most characteristic symptoms of ASD, suggest that an abnormality in the normal brain oxytocin system may underlie the disorder. This claim has recently found support from the genomic literature reviewed linking ASD to hypermethylation of the promoter region of the gene encoding the oxytocin receptor. These results also reconcile the disparity between the high heritability of ASD and the lack of genetic evidence to support it. Considering the evidence for an epigenetic mode of inheritance of maternal behavior in rats, it seems plausible that a similar epigenetic mode of inheritance may underlie ASD.

Although the etiology of ASD still largely remains a mystery, recent evidence has begun to shed some light on the issue. Converging evidence across multiple disciplines, including neuroendocrinology, genomics, molecular psychiatry, and other biomedical sciences suggest that the brain oxytocin system may underlie the abnormalities in social cognition characteristic of ASD. Although ASD shows high heritability, the disorder likely has an epigenetic rather than purely genetic basis. The oxytocin system may prove to be a fruitful target for researchers and physicians seeking novel treatments to improve the lives of both ASD patients and their families.

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