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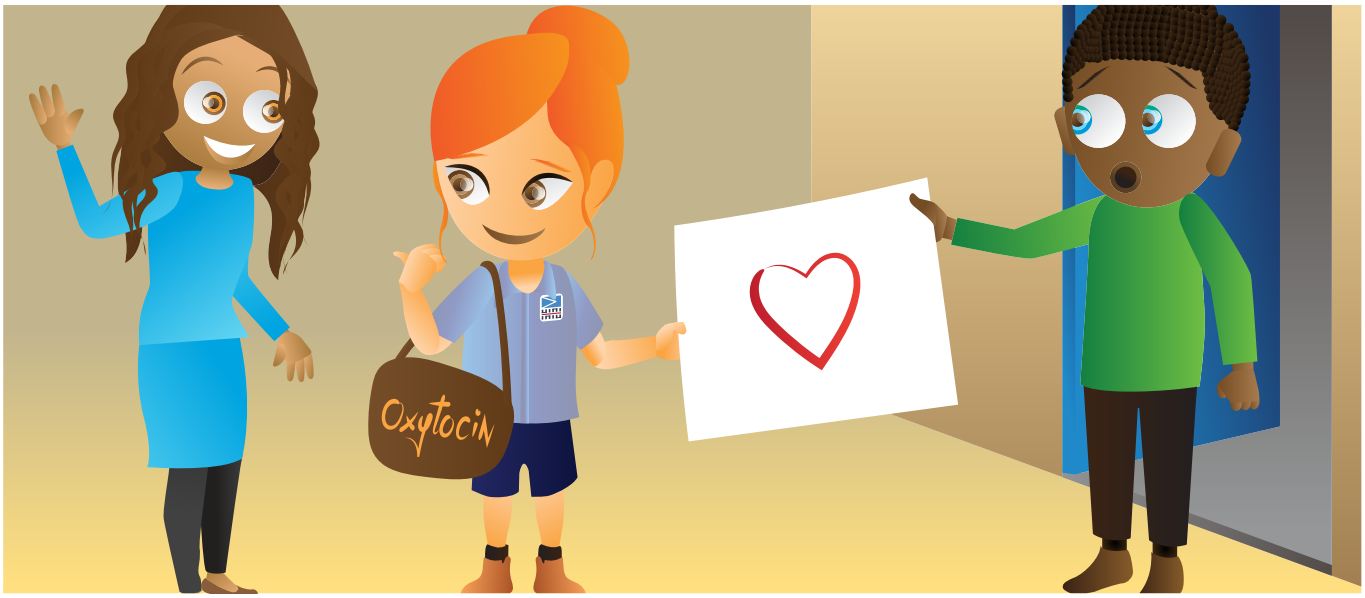

OXYTOCIN: HOW DOES THIS NEUROPEPTIDE CHANGE OUR SOCIAL BEHAVIOR?

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NEUROPEPTIDE

A small molecule naturally produced in the body that acts a messenger to trigger responses in our body, such as the feeling of hunger.

OXYTOCIN

A neuropeptide (see above) that is known to influence how we behave around other people.

Neuropeptides are small molecules that act as messengers between different brain regions. There are roughly 100 neuropeptides that are important for various functions, including hunger, memory, and learning. Oxytocin is a neuropeptide that plays a crucial role in childbirth and breastfeeding. More recently, oxytocin has been shown to be essential for our social behaviors. When given to people in the form of a nasal spray, oxytocin can change key aspects of social behavior, such as how easily we can recognize emotions in others. People with autism often have difficulties in understanding and using social information, and scientists have been testing oxytocin nasal spray as a potential treatment. But how does oxytocin nasal spray travel from the nose to the brain, and how does it change how we behave socially?

Neuropeptides are small molecules that act as messengers between different brain regions. There are roughly 100 neuropeptides that control various functions, including hunger, memory, and learning. **Oxytocin** is a neuropeptide that plays a crucial role in childbirth and breastfeeding. Oxytocin is produced in the hypothalamus, an almond-sized structure near the base of our brain. After production, oxytocin moves from the hypothalamus to the

rest of the brain, and throughout the body by way of the nearby pituitary gland (Figure 1).

There are millions of oxytocin receptors in the human body. These tiny receptors are like locks, and oxytocin is the key. When oxytocin unlocks the oxytocin receptors, these receptors become activated and trigger specific responses in the body. For example, during childbirth, the body releases a huge amount of oxytocin, which activates oxytocin receptors located on the mother's uterus (an organ located in the abdomen where the baby develops before birth). These receptors signal contraction of the uterus, which assists the baby's trip through the birth canal during birth. Later on, when a baby breastfeeds, oxytocin is released from the mother's brain to stimulate the flow of breast milk. If mothers are having difficulty in delivering the baby or with breastfeeding, their doctors will sometimes prescribe oxytocin (an artificial version that is sometimes delivered via a nasal spray) to help them with these processes. However, oxytocin does not just act in females – it is also involved in the control of blood pressure and kidney functions in both males and females.

WHAT IS THE ROLE OF OXYTOCIN IN SOCIAL BEHAVIOR?

Although the breastfeeding and birthing effects of oxytocin have been known for sometime, more recent research has shown that the oxytocin system is also

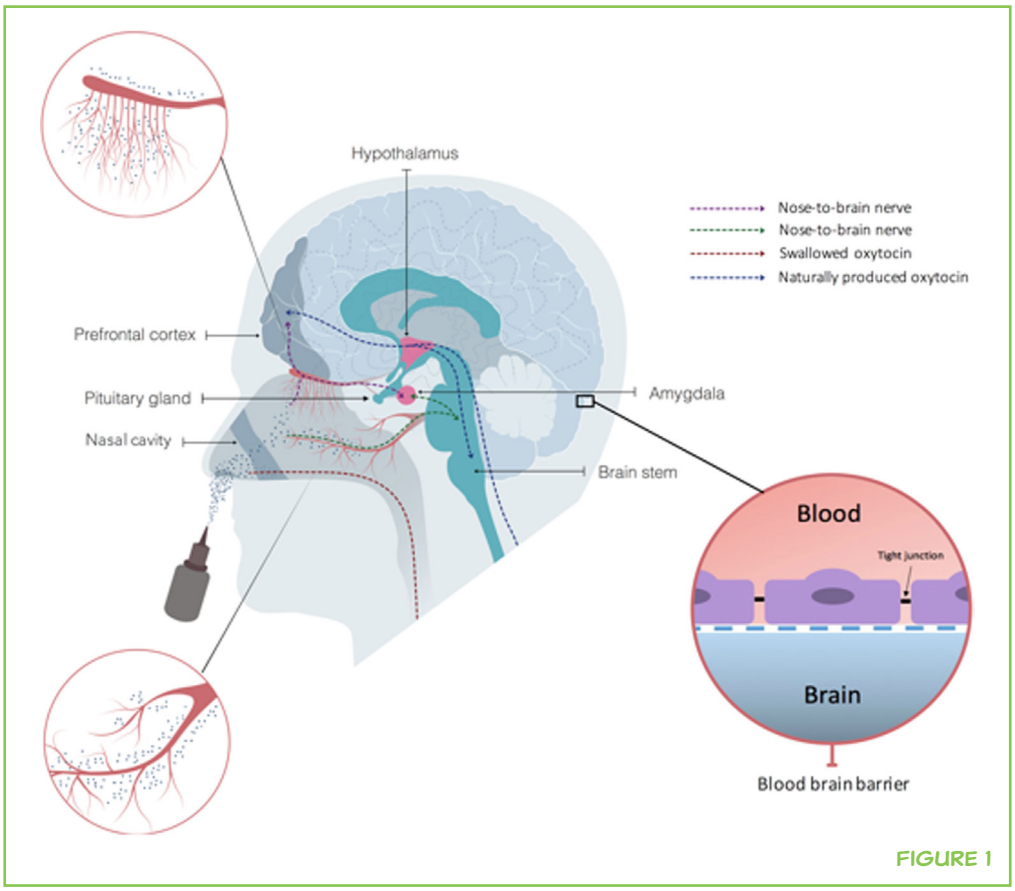

FIGURE 1

FIGURE 1

Oxytocin is naturally produced in a part of the brain called the hypothalamus and distributed both within the brain and to the rest of the body by way of the pituitary gland. Artificial oxytocin nasal spray is thought to access the brain directly through the nerves located inside the nasal cavity that are linked to the brain. Artificial oxytocin nasal spray has been shown to affect activity in different parts of the brain, such as the prefrontal cortex, amygdala, and the brain stem. The blood–brain barrier acts like a protective filter for the brain by preventing unwanted molecules entering the brain from the blood stream, but it can also prevent the entrance of large drug molecules, such as oxytocin. Small amounts of the oxytocin nasal spray are sometimes swallowed, which is relatively harmless. Image adapted from Quintana et al. [1].

important for how mammals develop and maintain complex interactions with other individuals (e.g., romantic relationships). These types of interactions are called **social behaviors**. The first clues for oxytocin's social role were shown with the help of animal research in 1970s and 1980s. Female rats do not pay much attention to rat pups that are not their own. However, giving oxytocin to female rats that have never had their own pups leads to an interesting reversal of this behavior. These female rats show mother-like behaviors, such as licking and nest building, toward pups that are not their own. Later, scientists turned their attention to **prairie voles**. These small mouse-like mammals are one of the few species (including humans) in which the male and female parents typically stay together to raise their young. Using powerful microscopes, scientists have shown that the brains of prairie voles have a large number of oxytocin receptors, especially within brain areas that are involved in social behavior. Further research has also shown that these brain regions are important for pair bonding, which is a term used to refer to how male and female animals often pair up to create and raise their children. However, the closely related meadow vole (Figure 2), which lives mostly alone, does not have as many oxytocin receptors in these social brain regions. In fact, blocking the effects of oxytocin in prairie voles reverses these pair bonding behaviors, demonstrating how important this neuropeptide is for social behavior [2]. Oxytocin (or closely related neuropeptides) has also been found to regulate social behaviors in various animals such as fish, birds, and snails.

SOCIAL BEHAVIOR

How we behave and interact with other people. This includes how we behave around one person (e.g., a friend or romantic partner) or a group of people (e.g., a class of children or a family).

PRAIRIE VOLES

A small mammal about the size of a mouse. Males and females typically stay together to raise their young, which is rare for animals.

WHAT ARE THE EFFECTS OF OXYTOCIN IN HUMANS AND HOW DOES IT WORK?

After seeing the effects of oxytocin on social behavior in mammals, researchers began to investigate whether these effects could also be observed in humans. At the same time, other research discovered that people with conditions that involve difficulties in social behavior (for example, problems in making friends

FIGURE 2

FIGURE 2

The meadow vole (shown here) and the closely related prairie vole (not shown) have been studied to learn more about social behavior in humans. Figure from Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Baby_meadow_vole.jpg

or forming romantic relationships) have lower levels of oxytocin in their blood compared with people without these conditions. Based on these results and the earlier animal research, scientists began to examine the effect of giving oxytocin to humans as a nasal spray. It was hoped that giving oxytocin as a medication might improve some social behaviors in people who have difficulties in these areas.

An important part of social behavior is understanding what other people are thinking or feeling. This ability is also known as "theory of mind," as it involves making sense of what is going on inside someone else's head. If we can understand others' thoughts or beliefs, and how this might be different from our own thoughts or beliefs, then we can better predict how we should interact with them or how they will behave in the future. Some of this information is transmitted without words, through body language. For example, we sometimes see sad people slump their shoulders forward. However, most emotional information comes from the face, particularly from the eye and mouth regions. For example, just from looking at the boy in Figure 3D, most people would view his smile and think that he is happy. The same boy in Figure 3E would be seen as angry due to his narrowed lips and his eyebrows being pulled down together. Most people can very easily and quickly understand the various types of emotional information shown in Figure 3. However, this skill can be limited or absent in some people.

To test if oxytocin improves the ability to understand emotional information, researchers gave adults oxytocin and then measured how they performed on a theory of mind test. This test presented photographs of the eye regions of different people and asked the participants to guess what each person was thinking or feeling. After taking oxytocin, compared to a control nasal spray that did not contain any oxytocin, people performed better on this theory of mind test [3]. Later research showed that this improvement is related to changes in the parts of the brain that are important for processing of social information. These regions have very high numbers of oxytocin receptors.

Although understanding these emotional clues from the eye region is important, people first need to pay attention to the eye region in order to even get this information. Many individuals who have difficulties in understanding emotions also spend less time looking at faces, particularly their eyes. By using

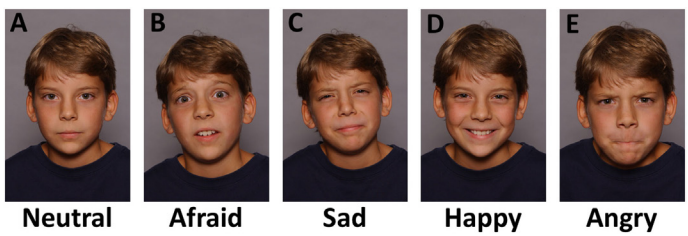

FIGURE 3

FIGURE 3

Most emotional information is broadcast from our faces. This boy is displaying various facial emotions; **A**. neutral/no emotion, **B**. afraid, **C**. sad, **D**. happy, and **E**. angry. Figures from the NIMH Child Emotional Faces Picture Set (NIMH-ChEFS) http://devepi.duhs.duke.edu/NIMH_Pictures.html

special cameras called eyetrackers that record exactly where people are looking (Figure 4), researchers tested which areas of the face people looked at the most after taking oxytocin [4]. They found that oxytocin increases the amount of time people spend looking at the eye region of these faces and decreases the time spent looking other regions of the face. Along with these effects, oxytocin has also been shown to change our social behavior. For instance, researchers discovered that giving people oxytocin increases loyalty toward their friends and families.

However, the effects of oxytocin are not all positive. Since this early research, scientists have learned that oxytocin influences *both* positive and negative emotions. For example, oxytocin administration has been shown to increase negative emotions, such as envy/jealousy, and the pleasure we get from witnessing the difficulties of others. Along with increasing cooperation with people in our own social group, oxytocin also decreases cooperation with those outside our social groups. So, rather than only being involved in "positive" social behaviors, oxytocin is more accurately described simply as a "social" hormone, responsible for many types of social behaviors, both positive and negative. There are two main ways that oxytocin is thought to effect our social behavior and understanding of social situations. The first way is by increasing how much we notice social clues around us, either positive or negative. The second is by increasing our desire to approach and interact with other people.

WHY USE A NASAL SPRAY TO DELIVER MEDICATION TO THE BRAIN?

Unlike most other medications, oxytocin is usually administered as a liquid spray into the nose. This medication is an artificial form of oxytocin that acts like the oxytocin naturally produced by the body. Medications targeted to the brain, such as antidepressants, are typically swallowed as a tablet or a liquid.

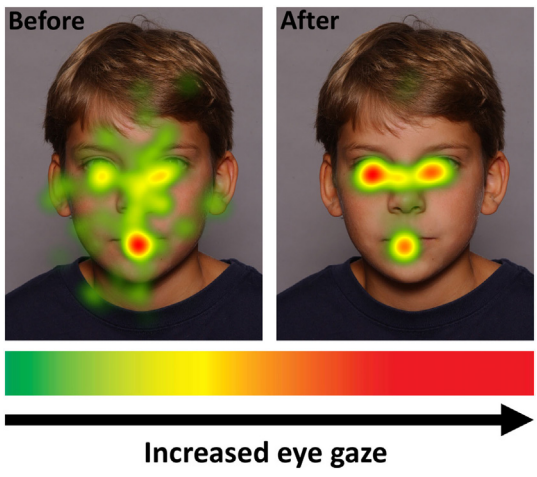

FIGURE 4

FIGURE 4

By using special cameras, eyetracker machines can record exactly where people are looking when they look at faces on a computer screen. A "heat map" can be constructed to visualize where people spend the most time looking, with the "hotter" areas receiving the most attention. The "before" face image on the left is represents the average eye gaze from a group of people with ASC before they were given oxytocin nasal spray, with little time spent looking at the eyes and more time toward other face areas. The "after" face image on the right shows the increased gaze to the eye region that has been reported after people with ASC are given oxytocin nasal spray. Adapted figures from the NIMH-ChEFS http://devepi.duhs.duke.edu/NIMH_Pictures.html

This usually works well, as small drug molecules can get into the bloodstream through the intestines and then slip through the barrier between the bloodstream and the brain. This barrier that surrounds the brain, also known as the **blood–brain barrier (BBB)**, acts like a protective filter by preventing unwanted molecules from entering the brain, but it can also prevent the entrance of large drug molecules, such as oxytocin. This means that oxytocin will never reach the brain by swallowing it as a liquid. Researchers sometimes inject oxytocin directly into the brain in studies using small mammals; however, this is not a good solution in humans, so other methods are needed.

BLOOD–BRAIN BARRIER (BBB)

A protective filter that prevents unwanted molecules from entering the brain, which could make us unwell.

The nose provides an effective route for medication delivery to the brain. The surface on the inside of our noses is an easily reachable area of the body that has a direct connection to the brain through a set of nerves (Figure 1). By spraying liquid medication into the nose, medications potentially avoid the BBB altogether. However, this spray needs to travel deep inside your nose – much deeper than your finger can reach – to reach the nasal regions that are linked to the brain.

Research has shown that the level of oxytocin in brain fluid increases after a person receives an oxytocin nasal spray. Although some side-effects have been reported (e.g., increased thirst), these are typically uncommon. Oxytocin nasal spray that does not reach the brain can also enter the bloodstream, although only very small amounts of oxytocin circulating in blood may actually cross the BBB into the brain. Therefore, the nose provides the easiest and safest way to get medications, such as oxytocin, to the brain.

OXYTOCIN AS A TREATMENT?

Some conditions, such as **autism spectrum conditions (ASC)**, are associated with poor social functioning. People who have ASC may experience difficulties in forming or maintaining relationships, can have trouble making eye contact, and may also have some repetitive behaviors (for example, lining toy cars up in a row repeatedly) or particular interests in very specific topics. It is important to note that autism is considered a "spectrum" condition, meaning that not all people with this condition are the same and that some symptoms can be more or less severe in any one person. For instance, people with ASC can have various intellectual abilities and can have many strengths in various aspects of their lives. However, many people with ASC experience significant difficulties with social behaviors, making it difficult to go to school, work, or have relationships. Unfortunately, there are currently no effective medications available to help with these social difficulties. Research in this area is still going on; however, some scientists have shown that when a single dose of oxytocin nasal spray is given to people with ASC, it can increase the amount of time they spend looking at other people's eyes and their ability to recognize emotions correctly.

AUTISM SPECTRUM CONDITIONS (ASC)

A group of complex conditions where people can have difficulties in forming relationships and communicating with others. These communication difficulties often include problems making eye contact or understanding other people's emotions. Repetitive behaviors (such as lining toy cars up in a row repeatedly) or particular interests in very specific topics are also commonly seen in people with an autism spectrum condition.

Although seeing improvement in specific social behaviors inside a laboratory is an important first step, research also needs to demonstrate that oxytocin nasal spray can improve day-to-day social functioning in the real world, with long-term daily use. Early research has shown that taking oxytocin nasal spray over 5 weeks led to small improvements in social behavior in young children with ASC [5]. However, other research in older children and adults with ASC has not shown any improvements after similar periods of taking oxytocin. So, it is still unclear whether oxytocin can actually help people with ASC by improving their social behaviors.

WHAT ELSE DO WE STILL NEED TO LEARN ABOUT OXYTOCIN NASAL SPRAY?

The fact that different studies have given different results tells us that we still have a lot to learn about how oxytocin influences behavior in humans. For example, the most effective nasal spray dose to use is still not known. In fact, we have found that a *smaller dose* may be more helpful than a larger dose [6] – bigger may not be better! Scientists are also still discovering exactly how oxytocin given through the nose might travel to the brain. The way that oxytocin is sprayed up the nose also influences its effects. The most commonly used nasal spray devices may not be the best method to deliver oxytocin, and new types of sprays that are better for delivering oxytocin to the brain are currently being tested [6]. Overall, it is clear that more work is needed to understand all the factors that influence the response to nasally delivered oxytocin.

CONCLUSION

Oxytocin plays an important role in social behavior and in the way we understand our social world. However, more research is needed before oxytocin can be used as a treatment for ASC, since scientists still do not have a clear understanding of how oxytocin works. Universities and hospitals around the world, including ours in Australia and Norway, are continuing to test the effectiveness of oxytocin on improving social behavior. This work will hopefully lead us to understand whether or not this hormone can help people with conditions like ASC at their school or workplaces and improve their relationships with other people.

AUTHOR CONTRIBUTIONS

DQ and GA conceived the manuscript idea. DQ drafted the work and GA revised it critically for important intellectual content. DQ and GA gave final approval of the version to be published and agree to be accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ORIGINAL SOURCE ARTICLE

Quintana, D. S., Alvares, G. A., Hickie, I. B., and Guastella, A. J. 2015. Do delivery routes of intranasally administered oxytocin account for observed effects on social cognition and behavior? A two-level model. *Neurosci. Biobehav. Rev*. 49:182–192. doi:10.1016/j.neubiorev.2014.12.011

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CONFLICT OF INTEREST STATEMENT: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ST. BERNARD REGIONAL CATHOLIC SCHOOL, 10–13 YEARS OLD

We are 10–13 years old students from St. Bernard Regional Catholic School. Although we are small, our knowledge is grand and our curiosity is unlimited. Many of us participate in different after-school activities, including Girl Scouts, Boy Scouts, sports, and music. We love doing science experiences and discovering new things in school. When we were approached to participate in an article review, we were so excited and oh boy, was it a great experience!

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I am an Australian researcher, now living in Norway. I study the role of hormones and physiology in psychological processes. I am especially interested in how both the oxytocin and cardiovascular systems influence our social behavior and perceptions. When I am not in the laboratory I enjoy traveling and being in the outdoors with my wife. *daniel.quintana@medisin.uio.no

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I am an Australian researcher, originally from Sydney and now living in Perth – the second most isolated city in the world! I work within a team of researchers investigating the underlying causes of autism spectrum disorder and testing new interventions. I am passionate about finding new and better ways to help children with autism spectrum disorder and their families lead fulfilling and happy lives.