

# Oxytocin & Cholesterol

Oxytocin is a hormone that has long been associated with uterine contraction during childbirth and milk let-down during nursing. While this description is basically correct, it does not explain why males have oxytocin, why increased oxytocin is often not detected during labour, or how oxytocin affects memory, stress responses and renal function.

The oxytocin and its receptor regulate social functioning in animals and humans. Initial clinical research suggests that dysregulated plasma oxytocin concentrations and/or oxytocin receptor mutations may be biomarkers of social impairments and

repetitive behaviours in autism spectrum disorder (ASD). There is increasing interest in oxytocin as a therapeutic approach to treating social deficits in ASD. Oxytocin has peripheral (hormonal) actions, as well as actions in the brain. The actions of oxytocin are mediated by specific, high affinity oxytocin receptors. The oxytocin receptor is a G-protein-coupled receptor which requires **magnesium and cholesterol**.

## Oxytocin - Some Current Known Functions

- ◆ Uterine contractions
- ◆ Bonding between mother and child during breast feeding, milk let-down
- ◆ Increases feelings of trust, pleasure and harmony
- ◆ Used to help with anxiety - **particularly social anxiety**
- ◆ Brain development for patterns of **facial and voice emotion recognition, social bonding**

## Oxytocin, Autism & Social Behaviour

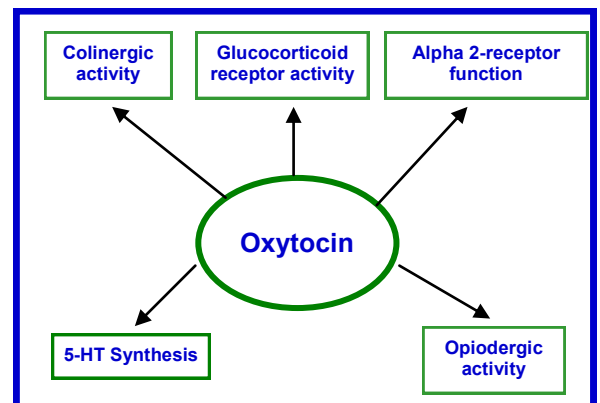
Given that oxytocin is involved in the regulation of repetitive and social behaviours, and that these are key features of autism, it is believed that oxytocin may play a role in autism, and that oxytocin may be an effective treatment for these two core symptoms in ASD. Studies of individuals with social phobia/ social anxiety disorder suggest a possible role for oxytocin in treating these social deficits in ASD.

## Oxytocin has wide ranging effects which include:

- \* Colinergic activity - which regulates stress
- \* Glucocorticoid receptor activity - controls the adrenals and the hypopituitary axis
- \* Alpha 2- receptor function - affecting the cardiovascular system
- \* Opioidergic activity - interacting with the opioid system
- \* 5-HT synthesis - serotonin production

Since oxytocin receptors are found throughout the body, it is not surprising that any dysfunction in

oxytocin production will affect the ability to deal with stress, and anxiety, as well as affect heart rate, and mood. With this in mind, it is likely that impairment in the oxytocin system contributes to many of the symptoms of ASD.



## Role of Oxytocin in ASD

Studies of oxytocin in ASD individuals has shown:

- ◇ Lower levels of serum oxytocin compared to controls
- ◇ Higher levels of oxytocin precursor levels
- ◇ Specific variants of the oxytocin receptor genes
- ◇ Heightened amygdale activation (to faces with a direct gaze) which oxytocin is able to inhibit

Studies have shown that impairments to oxytocin production or receptor function affects:

- ⊗ Poor facial pattern recognition
- ⊗ Poor social cue recognition
- ⊗ Difficulty with coping skills
- ⊗ Ritualistic and repetitive behaviour
- ⊗ Poor social interaction and bonding interests or skills
- ⊗ Anxiety, aggressiveness, irritability, etc.

With anxiety comes the ritualistic and repetitive behaviour.

ASD is linked to both lower levels of oxytocin and mutations in the oxytocin receptor, so oxytocin is unable to bind efficiently. This receptor is where oxytocin binds to its appropriate neuron and causes it to fire. If the neuron is involved in filtering out unnecessary information (background noise) and highlighting important information then it will fail to be effective. Although many ASD individuals learn to compensate by learning to develop rules to follow, this requires incredible effort on their part. During social stress, oxytocin helps to decrease secretion of adrenocorticotrophic hormone (ACTH), cortisol and catecholamines, thereby increasing the ability to interact socially. Also there are signalling molecules called, **extracellular regulated kinases (ERKs)**, that seem to increase the brain's response to fear, particularly from past negative experiences. Oxytocin can up regulate these molecules, which causes an increase in fear and anxiety, and may explain why a sub-group of individuals react badly to administered oxytocin.

## The Link Between Oxytocin and Cholesterol

Here is yet another interesting piece of research and feedback from clinic observation that is not widely known. Cholesterol is continuously in the news as being bad and doctors are prescribing statin drugs to lower cholesterol levels. We all know the risk of having very high cholesterol. However, research that has been "buried" in the literature clearly shows that low levels of cholesterol are responsible for increased risk of violent behaviour, depression, infection, stroke and even cancer.

What do some of the studies of low cholesterol levels indicate:

- \* Children having adjustment disorders with depression have much lower cholesterol levels than control school age children
- \* These children have higher suicide tendencies (attempts and ideation)
- \* Substance abuse is inversely linked to low cholesterol levels as well as tendency to relapse
- \* Hospitalised patients who attempted suicide have significantly lower levels of cholesterol, that is not influenced by age, sex, ethnicity, weight, disease severity, or physical health
- \* In one study non-African American children with a serum total cholesterol concentration below the 25% of normal range were **almost three times more likely to have been suspended or expelled from school than controls with higher cholesterol levels.**

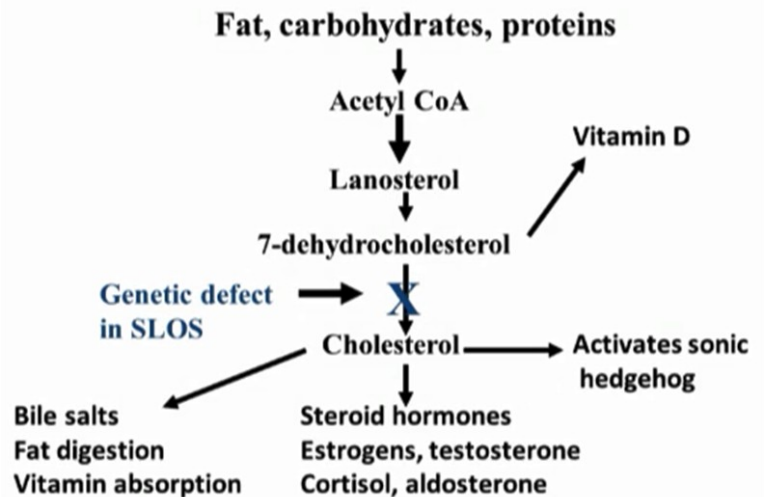
## What are some functions of cholesterol?

- ✓ It is a structural component of animal cell membranes, providing membrane fluidity and permeability.
- ✓ It is a large component of myelin protecting nerve cells
- ✓ A precursor to the production of steroid hormones (ie. oestrogen, progesterone, testosterone and cortisol)
- ✓ Needed for the production of bile acids and absorption of fat soluble vitamins A, D, E, and K.
- ✓ Involved in the production of vitamin D in skin via sun exposure

Low cholesterol causes **reduced binding of serotonin to the serotonin A1 receptor and G-protein coupling.**

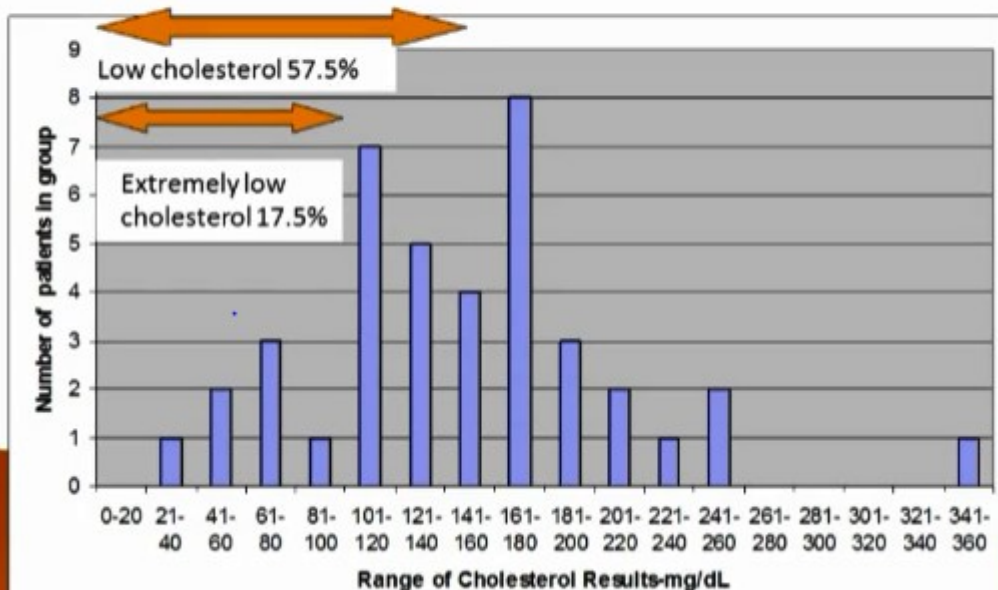
Receptors play an important role in the brain and other organs, regulating temperature control, sleep, anxiety, aggression, and eating. **Smith-Lemli-Opitz Syndrome (SLOS)** is a disorder of 7-dehydrocholesterol reductase deficiency, an enzyme that is involved in the last step of cholesterol production. Therefore, individuals with this enzyme defect have elevated levels of 7-dehydrocholesterol, the precursor to cholesterol in their blood.

## Formation of cholesterol



There is some overlap in the symptoms of SLOS and ASD. Some of the symptoms that characterise the syndrome include: lack of speech, severe behaviour abnormalities (frequent temper tantrums, hyperactivity, violent outbursts, destruction of property, self-mutilation), and UV-light sensitivity. Supplementing these children with adequate cholesterol sees a significant improvement in symptoms.

## The Great Plains Laboratory cholesterol study of children with autistic spectrum disorder



The above figure is from the Great Plains Laboratory, which shows cholesterol levels collated from ASD children. From their data it is clear that there is a significant percentage of children that are low in cholesterol. Some studies have also shown higher levels of the cholesterol precursor 7-dehydrocholesterol in the blood of ASD individuals.

### What do we see when SLOS individuals are supplemented with adequate cholesterol?

- ✓ Begin to walk
- ✓ Start to run
- ✓ Improvement in growth
- ✓ Less susceptibility to infections
- ✓ Increased alertness
- ✓ Head banging stops
- ✓ Decreased tactile defensiveness
- ✓ Increased sociability
- ✓ Behaviour improves
- ✓ Talking has started in adults who were not talking before
- ✓ Verbal individuals report that they “feel better”
- ✓ Decreased irritability
- ✓ Increased muscle tone
- ✓ Less UV sensitivity

### What are the Potential Causes of Low Cholesterol in ASD

- Hypothyroidism
- Malabsorption of nutrients from the gastrointestinal tract
- Malnutrition
- Chronic gastrointestinal infections
- Manganese deficiency
- Possibly genetic enzyme polymorphisms

### Why would cholesterol have some of these beneficial effects?

Cholesterol increases binding of serotonin to the serotonin A1 receptor. It is also involved in cell membranes, which increases flexibility and pliability. It is estimated that up to 70% of the brain cholesterol is associated with myelin. Why would we see an increase in sociability? Potentially cholesterol can up regulate oxytocin receptors. The affinity of the receptor to bind oxytocin is dependent on cholesterol and magnesium. Also cholesterol protects the G-protein-coupled oxytocin receptors against loss of function. Cholesterol also delays the inactivation of oxytocin receptors. Basically, oxytocin works better in the presence of cholesterol as the oxytocin receptor is stabilised and function is enhanced. Possibly in the studies that ASD individuals do not improve with a trial of oxytocin, they may be low in cholesterol and or magnesium. Indeed these may also be the individuals that react badly to oxytocin. The research has not been done, so we do not know.

### What are the clinical trials of nasal oxytocin telling us?

Some of the clinical experience that is being reported from clinical studies includes:

- ✓ Improved interest in socialisation, more playful
- ✓ Decreased repetitive behaviours
- ✓ Decreased overall anxiety, calmer
- ✓ Some heightened sexual interest (adults)
- ✓ Onset of benefits within 15 to 20 minutes in many cases



## Oxytocin Preparations

If you are considering a trial of oxytocin, oxytocin is a scheduled product and requires a doctor's script.

**Compounded oxytocin intranasal sprays.** In the USA, Syntocinon produced by the drug company Novartis, has been the oxytocin intranasal spray used in clinical trials. Novartis withdrew the product for "commercial reasons", some time ago. However, the company Retrophin, has acquired the exclusive license and will continue to supply the product for clinical research.

In Australia, oxytocin intranasal spray is available through some compounding pharmacists. Anyone interested in doing a trial of oxytocin can contact me for details of a reputable compounding pharmacy, experienced in preparation and dosing of oxytocin for ASD patients.

**Oral and sublingual tablets** are also available, however the intranasal route seems to be the preferred way of administering the dose of oxytocin. It is metabolised quickly, giving more immediate effects.

Oxytocin is destroyed in the gastrointestinal tract, and therefore must be administered by injection or as a nasal spray. Oxytocin has a half-life of typically about three minutes in the blood.

## Homeopathic Oxytocin

Due to the reasonably high cost of pharmaceutical oxytocin and nasal delivery may be an issue for some children, some parents choose to try homeopathic oxytocin. Homeopathic oxytocin is available in convenient liquid drops or as small pills.

## Dose of Oxytocin

The dose of oxytocin prescribed is usually between 10 and 40IU/mL, however higher doses have also been used by practitioners.

## Cholesterol Supplementation

The dose is dependent on the level of total cholesterol as measured in the blood. For low normal cholesterol levels, suggested dose is 500mg in divided doses with meals. Very low levels require higher doses as determined by your practitioner.

## What Other Hormones May be Involved in Social Phobia and Autism?

### Cortisol

Shy children and children with behavioural inhibition typically have higher cortisol levels.

### Growth Hormone

One study reported the incidence of social phobia (38%) in individuals with a growth hormone deficiency, who were treated with growth hormone in childhood. Another study found that people with social phobia had a blunted response to growth hormone. The mechanism for this observation is not known.

### Adrenocorticotrophic hormone (ACTH)

Autistic children treated with a synthetic analogue of ACTH for 4 weeks showed increased and improved quality of social interaction (more eye contact, mutual smiling, and decrease in stereotyped behaviours). Higher plasma levels of ACTH have been found in ASD individuals compared to controls. This could be due to chronic hyperarousal, or acute hyperarousal in response to stress. It is thought to be the latter as many studies have reported normal baseline functioning of the HPA axis.

## My clinical experience using oxytocin in ASD children

I have had patients on both the pharmaceutical oxytocin intranasal spray and the homeopathic oxytocin. The oxytocin intranasal spray does need a doctors script, which I help parents obtain by liaising with their doctor informing them about the studies of oxytocin in clinical trials and the recommended dosages. Most family doctors do not seem to have a problem with approving the oxytocin script. As for the effects of the intranasal spray, I see the same as in the clinical studies. Results are variable. I have had one child where the mother reported amazing improvement in the ability to initiate reciprocal speech. Interestingly, when the oxytocin was stopped, the child retained all the initial benefits. It was as if a “switch” had been activated somewhere in the brain. Some of the more recent studies report that the effects of oxytocin may be maintained for up to 3 months.

More recently, I have begun to trial homeopathic oxytocin as reports from some US doctors have been positive. So far I am seeing the same variable results as with the pharmaceutical product. Nevertheless, we are seeing positive results in a sub-set of children. In light of the connection with cholesterol, in future I will be assessing patients for low cholesterol levels and magnesium, prior to supplementing with oxytocin to see if there is an added benefit.

I have heard of some Biomedical doctors who specialise in treating ASD children, combining oxytocin and secretin as an intranasal spray. However, I haven't seen any published studies that are using a combination of oxytocin and secretin.

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## Additional Research on Oxytocin

Recently there has been a significant increase in the number of published studies on oxytocin (OXT). Below are just some of the areas of oxytocin research that are evolving.

### Oxytocin receptor Gene Polymorphisms

The oxytocin receptor gene (OXTR) is being studied as a risk factor in ASD. Studies are now focussed on elucidating which OXTR single-nucleotide polymorphisms (SNPs) are associated with ASD. There have been a number of OXTR SNPs that seem to be significantly associated with ASD.

One study looked at whether OXT dysregulation is unique to ASD or whether OXT biology influences social functioning more generally, thus contributing to, but not causing, ASD phenotypes. Their findings indicated that OXT biology is not uniquely associated with ASD, but instead exerts independent, additive, and highly heritable influences on individual differences in human social functioning, including the severe social impairments which characterise ASD.

### Brain Imaging Studies

Functional magnetic resonance imaging (fMRI) of the brain following oxytocin administration have been shown to have specific effects in the brain of ASD individuals. The amygdala appears central in the regulation of serotonin by OXT. OXT increased binding in the dorsal raphe nucleus (DRN), the core area of serotonin synthesis which correlates with changes in hippocampus, insula, subgenual, and orbitofrontal cortex, a circuit implicated in the control of stress, mood, and social behaviors. [OXT administration is known to inhibit amygdala activity and results in a decrease of anxiety](#), whereas high amygdala activity and serotonin dysregulation have been associated with increased anxiety.

### The Oxytocin Paradox

Despite positive effects on social behaviour, there has been considerable speculation about OXT's therapeutic potential in people with social and emotional disabilities. This pro social view of OXT has been challenged by findings showing that the effects of OXT are strongly context dependent. For example, "OXT has also been shown to increase envy and gloating, defensiveness toward out group members and increased in group conformity". This paradox gives rise to two questions. First, how can the beneficial effects of OXT on empathy, trust and affiliation be compatible with its seemingly contradictory anti-social effects? Second, what implication does this have for the therapeutic potential of OXT in social and emotional neurodevelopmental conditions? These are still questions for future directions into oxytocin research.

### Ongoing studies

A review of oxytocin interventions in autism concluded potentially promising findings in measures of emotion recognition and eye gaze. Future studies should try to enrol female participants, who were rarely considered in previous studies.

In another trial of over 12 weeks of oxytocin treatment, several measures of social cognition/function, repetitive behaviours and anxiety showed positive change [with some measures suggesting maintenance of effect 3 months past discontinuation of intranasal oxytocin](#). No serious or severe adverse events were reported and adverse events reported/observed were mild to moderate. The study suggests that daily administration of intranasal oxytocin at 0.4IU/kg/dose in children and adolescents with ASD is safe and has therapeutic potential.

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