The Classical Neurohypophyseal Hormones Have Considerable Potential For Modifying Human Behavior

J Joshi, S Dindyal

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Abstract

Oxytocin (OT) is a nonapeptide, mammalian hormone that is principally manufactured in the magnocellular neurons of the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei. The majority of the peptide is transported to and released from the posterior pituitary gland (neurohypophysis) and is best recognised for its role in the regulation of parturition and lactation. In non-human mammals, the OT receptor (OTR) has been found to be distributed in various regions of the brain (1) associated with social behaviour and the central nervous control of stress and anxiety. OT has also been demonstrated to possess significant binding capabilities in the limbic system (including the amygdala) (2) and attenuates anxiety and the neuroendocrine stress response (3). More recently, OT has been implicated in having a role on human behaviour and a number of studies have identified some similarities between non-human mammals and humans in terms of brain region activation/inhibition.

Animal studies have shown OT to have behavioural, stress-reducing and anxiolytic effects (4); a study by Parker *et al.* demonstrated that intracerebral OT inhibits the responsiveness of the stress-activated hypothalamic-pituitary-adrenal (HPA) axis (3) and a study by Huber *et al.* showed that intracerebral OT inhibited the activity of the amygdala in the modulation of the autonomic fear response (2). Based on these findings of OT's effects on prosocial behaviour, the neuroendocrine responses to stress and other previous animal studies, research into whether OT plays a major a role in behaviour in humans could then be carried out. A study by Heinrichs *et al.* looked at the role of OT in conjunction with social support on mood, anxiety and responses to psychosocial stress in humans. A double-blind, placebo controlled study was carried out in which 37 healthy men were randomly assigned to receive intranasal OT or a placebo 50 minutes before the stress (Trier Social Stress Test) with either social support from a friend or no support all during the preparation period. The subjects who received both social support and intranasal OT displayed the lowest cortisol concentrations (a measure of stress), increasing calmness and decreasing anxiety scores during stress exposure and those that did not receive any social support and had the placebo demonstrated the highest levels of cortisol, a decrease in calmness and increase in stress, as expected. In addition to these results, pre- and post-stress comparisons of anxiety displayed that OT administration produced an anxiolytic effect and that OT further strengthens the anxiolytic effect of social support (5). Another study that further highlights the importance of OT's role as a system for stress-protective effects of positive social relations is one carried out by Ditzen *et al.* This team carried out a study on behaviour during couple conflict and showed that intranasal OT significantly increased positive communication and related behaviours like eye contact and positive body language between couples during a conflict discussion; this was found to be true for both men and women. They concluded that OT did not increase positive behaviour in total but increased positive behaviour in relation to negative behaviour. In addition to these findings, the stress-induced cortisol response was also found to be reduced, further emphasising OT's role in attenuating the neuroendocrine stress response (6).

Another mechanism by which OT modulates behaviour is through the reduction of activity of the amygdala in the modulation of the autonomic fear response. The amygdala expresses a variety of neuropeptide receptors (2), including those of OT (7). Fear detection involves the lateral and basolateral parts of the amygdala and detection of a fear stimulus leads to potentiation of synaptic transmission. The lateral and basolateral parts project to the central amygdala whose efferents to the brainstem and hypothalamus trigger

the autonomic expression of fear (8)(2). The study aforementioned carried out by Huber *et al.* which was carried out in rodents, provides evidence to show that the output from the amygdala to the brainstem which brings about a fear response to an adverse stimulus is reduced in response to OT binding to its receptors in the amygdala, i.e. OT dampens down the autonomic fear response (2). A subsequent study in humans was to follow on from this discovery in rodents. Kirsch *et al.* carried out an investigation to see whether the reduced activation of the amygdala observed in non-human mammals also occurred in humans. Functional magnetic resonance imaging (fMRI) was used to image amygdala activation in 15 healthy males when exposed to fear-inducing visual stimuli after a double-blind crossover intranasal administration of placebo or OT. The results of the study showed that OT significantly reduced amygdala activation and also reduced coupling of the amygdala to the brainstem regions involved in autonomic and behavioural expressions of fear (9). Therefore these results are in correlation with the non-human mammals' results, further implicating OT's role in the modification of human behaviour.

There has also been some recent work looking into OT's role in promoting sociability, more specifically by increasing feelings of trust. A trust game used by Kosfeld *et al.* was used in a behavioural study and showed that intranasal OT greatly increased trust between humans. 45% of the subjects in the OT group exhibited the maximal trust level, whereas only 21% in the placebo group reached this level. The study also showed that OT's effect on trust is not due to general increase in inclination to bear risks but is due to an increment in an individual's willingness to acknowledge social risks that have arisen through interpersonal interactions (10)(11). A consequent study carried out by Baumgartner *et al.* used fMRI to analyse the effect of OT on the neural circuitry involved in trust behaviour. A similar trust game to Kosfeld's study was used but some modifications were incorporated into the game whereby a subject's initial trusting behaviour was 'betrayed'. The results displayed that intranasal OT increased an individual's tolerance to the betrayal of trust (when compared to a placebo) and the fMRI scans showed that this adaptation was linked to a decrement in activity within the areas of the brain involved in emotional processing such as the amygdala (12). Again it is evident to see that OT is playing a somewhat significant role in human behaviour by altering the activity of the amygdala. The studies carried out by Kirsch and by Baumgartner have both come to the conclusion that OT is reducing output from the amygdala to promote positive social behaviour.

More recently, researchers have begun to explore the effects of OT on human social recognition, principally by testing recognition of faces. As with some of the previously mentioned effects of OT on behaviour, the actions of OT on social recognition had already been investigated in rodents; OT was found to enhance social recognition, indicated by a decreased investigative behaviour towards a particular rodent during a second encounter (13,14). It is also quite fascinating to note that in OT knockout mice, social memory is impaired, however a single injection of OT before an initial social encounter will restore social memory (14). Furthermore, something even more remarkable is that these knockout mice have no shortfalls in nonsocial memory (15). This is highly indicative of OT modulating only social but not nonsocial memory. A study carried out by Savaskan *et al.* looked into the short- and long-term effects of intranasal OT on memory for facial identity and also facial expression in 36 healthy human females and males. OT was administered intranasally to the subjects after viewing male faces either with a happy, angry or neutral expression and it was found that OT significantly improves recognition memory 30 minutes and also 24 hours after the test but only for neutral and angry facial expressions, not happy facial expressions (16). In contrast to this, a study by Guastella *et al.* showed that administration of intranasal OT given before viewing the faces enhances recognition memory for happy facial expressions compared to angry and neutral facial expressions (17). A study carried out by Rimmele *et al.* was the first to demonstrate that OT enhances facial recognition but not for nonsocial stimuli in humans. Their study showed that a single dose of intranasal OT 40 minutes prior to the viewing of the different faces produced a noteworthy improvement in the ability to recognise faces 24 hours later and in the meantime the recognition of nonsocial stimuli was left totally unaffected (18). Rimmele's findings are consistent with those of Savaskan and Guastella that suggest an overall enhancing effect of OT on processing of face stimuli. Also more importantly, Rimmele's results are concurrent with those obtained from the rodent studies. Recognition of individuals is an important part of everyday life. If one did not possess the ability to differentiate a friend from a stranger, it would be difficult to display the appropriate behaviours towards them, The creation of a social memory of individuals is therefore crucial and OT is essential in regulating social memory but not for learning of nonsocial information/stimuli (18).

For more than a decade a number of studies have connected OT with pair-bonding. It is well established that OT plays a significant role in pair-bonding in prairie voles. One study carried out by Williams *et al.* demonstrated that OT infusion into the cerebral ventricles of female prairie voles sped up the pair-bonding process; these female voles only required a brief encounter with a male (without mating) to form a partner preference (19)(20). In contrast, one study found that OTR antagonists prevented partner preference pair-bonding in prairie voles (21) and another found that OTR antagonists applied directly to the prefrontal cortex or nucleus accumbens (of female prairie voles), where there is an abundance of OTRs, inhibited mating-induced partner preference formation (22). This demonstrated that OTR activation in these brain regions is necessary for developing partner preferences in prairie voles (23). As prairie voles are monogamous, they can therefore be likened to humans in terms of bonding and mating behaviour. It is intriguing to consider the likelihood that similar mechanisms may underlie the formation of pair-bonds in humans as well as rodents. Anatomical and pharmacological studies have demonstrated that the nucleus accumbens, prefrontal cortex and ventral pallidium are all vital brain regions involved in pair-bond formation. Interestingly, these same regions are affiliated with the mesolimbic dopamine reward system, hinting that perhaps pair-bond formation uses the same neural pathways as reward. Human imaging studies have provided evidence consistent with the idea that neuropeptide and reward pathways are involved in human pair-bonding; when human subjects viewed photographs of people they were romantically in love with, their brain activity (measured by fMRI) looked strikingly similar to those observed after cocaine or opioid intake with heavy activation of the striatal dopamine regions and ventral tegmental area (24). Many of the activated regions are abundant in OT or OTRs (25,26). This evidence suggests that OT has yet another role in modulating human behaviour, this time in pair-bond formation and mating behaviours. However, it remains unconfirmed as to whether this link between the neuropeptide and reward pathways is responsible for pair-bond formation. Further investigation is needed.

In terms of a person's mental state and health, social behaviour is tightly regulated and any disturbances in this may result in a psychopathological state. Social deficits are associated with a group of disorders known as autism spectrum disorders (ASD) to which autism and Asperger's syndrome belong to. ASD are portrayed by a particular pattern of abnormalities in communication, social cognition and repetitive behaviours (11). Recently, a number of these social abnormalities and deficits present in ASD have been compared to the behaviour of animals that lack OT, leading to some suggestion that there may be a link between ASD and OT (27). The positive effects of OT on the formation of social bonds in animal studies have also led many to believe that OT abnormalities are playing a part in autism. There is some evidence linking OT levels to autism. OT levels in blood plasma of autistic boys was shown to be reduced compared to a group of age-matched controls (28) and infusions of synthetic OT notably reduced repetitive behaviours such as repeating and self-injury in patients with autism and Asperger's Syndrome (29). Even though the plasma OT data is in correlation with the hypothesis that alterations in the OT system are playing a role in the social behavioural phenotype in autism, it must be taken into account that the differences in OT levels may be due to altered cognitive processing in autistic patients. The change in processing of social stimuli that result from distorted wiring of the brain may prevent the normal activation of the OT system, ultimately producing a decreased plasma concentration. There is also some moderate evidence linking the OTR gene with autism; some studies indicate that single nucleotide polymorphisms in the OTR gene are linked with ASD. One study in particular carried out by Wu *et al.* reported a significant positive association of the OTR gene with autism in a Chinese Han population (23,30). These studies and various others have given insight into how OT may modulate human behaviour to cause mental disorders like ASD. However, even though these links between OT/OTR and ASD are promising, it is important to bear in mind that a variety of gene systems in a number of different combinations contribute to an observable phenotype and many other systems are currently being explored in relation to autism so all of the answers have not yet been revealed as to what OT's specific role is and what interactions (if any) it is having with other systems.

In conclusion, numerous animal studies of OT's effects on behaviour have allowed us to apply these findings to human studies and see whether OT is having the same behavioural effects. OT appears to have an important role in the regulation of the behavioural and endocrine stress response; it is shown to have a calming/ anxiolytic effect during stress and dampening effect on the autonomic fear response. OT also appears to have positive effects on social approach behavior and affiliation and the associated cognitive processes in humans; it increases an individual's trust, greatly enhances social recognition/memory and encourages

positive interaction. These behaviours are vital for everyday life further emphasising how important a role OT is playing in human behaviour. A common factor present in all of these effects is OT's effect on the amygdala. OT appears to have an inhibitory effect on the amygdala, promoting prosocial and stress-reducing behaviour. OT's effects on pair-bonding and relations to mental health disorders are less well established but research that has recently been carried out is positive and research in the near future could yield better results to improve our knowledge on the complexity of OT's actions. OT's anxiolytic and socially enhancing effects have also demonstrated that OT could be an important therapeutic target in a number of mental conditions like ASD which are characterised by an impairment of social interaction and communication. Although all of these discoveries are promising, much more investigation is needed.

References

Author Information

J. Joshi, BSc (Hons)(Lond), MB BS (Hons)(Lond)
Princess Alexandra Hospital NHS Trust, Princess Alexandra Hospital
Harlow, Essex, United Kingdom
jayjoshi20@gmail.com

S. Dindyal, BSc (Hons)(Lond), MB BS (Hons)(Lond), MRCS (Edin), MRCS (Eng)
Barts and The London NHS Trust, Barts and The London School of Medicine and Dentistry, Circulatory Sciences Clinical Academic Unit, Vascular and Endovascular Surgical Services, The Royal London Hospital
London, United Kingdom
doctordindyal@hotmail.com