Postnatal depression, oxytocin and maternal sensitivity

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General Discussion

Research exploring the role of oxytocin in parenting behavior, had its genesis in animal research. An increase in plasma oxytocin after cervical stimulation in ewes resulted in non-rejecting maternal behavior towards alien lambs even after selective bonding with their own lambs had occurred. The same stimulation also led to commencement of maternal behavior in cycling ewes [201]. Oxytocin plasma concentrations in reproductively naïve male prairie voles, after twenty minute exposure to a pup, increased [202]. Female prairie voles given oxytocin improved their alloparenting behavior [203].

Findings from animal models prompted research in the field of human behavioral science. In humans, intravenous oxytocin has been delivered to a population with a diagnosis of autism, with central effects being found [204, 205]. More commonly, administration of oxytocin via the intranasal route has occurred to ascertain its effect on numerous social outcome measures (e.g., [15, 124, 199]). However, questions remain unanswered regarding the pharmacokinetics involved. The oxytocin molecule doesn't easily cross the blood brain

barrier [206], but has been shown to reach the brain in animal studies [207], with an uptake ratio of about 2% [208] and produce central effects in humans, [122, 123, 206, 209] such as the down regulation of amygdala activation, when delivered intranasally. What remains unknown is the mechanism of this action. Various pathways have been postulated, such as direct diffusion from nasal cavity to cerebrospinal fluid [210] or an indirect peripheral mechanism [206].

Accepting this mechanistic black-box, this thesis broadly explored the associations between oxytocin, maternal sensitivity, maternal protectiveness and postnatal depression in humans. Oxytocin is a neuropeptide produced centrally (but not exclusively) in the paraventricular and supra optic nuclei. It acts in many physiological processes including delivery [9] and breastfeeding [10], it aids social affiliative processes [11] and is involved in parenting behaviors [12] including bonding [119]. Maternal or parental sensitivity is a construct incorporating the ability of a caregiver to accurately perceive and interpret an infant's signal and then the skill

and motivation to choose and carry out an appropriate caregiving response [182]. Mothers vary in their caregiving sensitivity, and those who display high maternal sensitivity are more likely to have an infant with a secure attachment and better academic outcomes [116, 183-185]. Maternal protectiveness, or maternal aggression, as it is referred to in animal literature, is considered an essential component of adequate parenting [165]. This aspect of parenting has been far less focused upon in human studies, however similarities between human mothers' protectiveness of their infants and animal maternal aggression has been commented on [166]. Postnatal depression is a high incidence psychiatric disorder [1] and results in many negative outcomes for the infant [2, 195].

Initially a comprehensive introduction to the topic is provided (Chapter 1). A systematic review was carried out with the aim to understand associations in the following three topic areas: i) postnatal depression and its impact upon parenting, ii) oxytocin and parenting and iii) postnatal depression and oxytocin. This review sought to answer four related questions. Does depression affect the quality of

parenting? Do interventions in a depressed cohort improve parenting? What is the effect of oxytocin on parenting in a community sample? What effects, if any, has oxytocin on postnatal depression?

Chapter 2 considers the effect of administration of oxytocin to a group of mothers with postnatal depression on their mood, Expressed Emotions and verbal fluency. Chapter 3 explores how mothers with postnatal depression behave with respect to their level of protectiveness towards their infant after intranasal oxytocin administration. Chapter 4 reports on study findings which sought to confirm our hypothesis that oxytocin administration to a sample with postnatal depression would improve aspects of sensitive parenting especially if the mother had experienced a supportive childhood. The findings will now be discussed in greater detail.

Mood, Expressed Emotion and Executive Function

The overall hypothesis for this thesis was that oxytocin provided to a sample of mothers with postnatal depression would result in increased caregiving sensitivity. We aimed to break down

aspects of sensitive parenting into relevant components. This chapter explores the mothers' mood, her representations or interpretations of her infant and her executive or frontal lobe function. We considered all these aspects important for caregiving as a sensitive mother has to be in a mood state conducive to response, she needs the ability to both attend to her infant and plan an adequate response and she needs to interpret her infant's communicated need. Twenty-five mothers with postnatal depression with infants under the age of one, participated in a randomized, double-blind, placebo-controlled within-subject clinical study. They received 24IU of oxytocin alternating with placebo approximately one week apart in random order, forty-five minutes prior to completing outcome measures. The diagnosis of depression was initially made by clinical interview but severity and currency of symptoms were established by use of the Edinburgh Postnatal Depression Scale [99], immediately prior to laboratory sessions. The outcome measures were the Self-Assessment Manikin to measure mood [149], the Five Minute Speech Sample which measures Expressed Emotion [130], and the Controlled Oral Word Association Test to examine executive function [150]. In the

oxytocin condition mothers reported feeling sadder. They more often initially described their babies as difficult but reported that the quality of their relationship with their infant was more positive. There were no significant findings when measuring performance on the Controlled Oral Word Association Test for the oxytocin compared to the placebo condition.

This chapter also considers whether there are differential effects of oxytocin, as other studies have found [102, 104, 146], depending upon the quality of childhood the participant experienced. We measured rates of childhood trauma using the Conflict Tactic Scales: Parent and Child Version [148, 152]. We did not find a moderating effect of a childhood history of severe physical abuse on any of the outcome measures.

Maternal Protectiveness

Chapter 3 explores the effects upon maternal protectiveness of intranasal administration of oxytocin in mothers with a diagnosis of postnatal depression. Successful parenting requires parental behaviors that ensure infant survival such as protection from predators. In animal studies, oxytocin has been associated with

maternal aggression to protect offspring [163]. This chapter presents the first findings exploring this topic with human participants (to the best of our knowledge). It is particularly important to consider this in a clinical population as mothers with a diagnosis of postnatal depression are at higher risk of neglecting their infants [164].

Mothers with a diagnosis of postnatal depression received 24IU intranasal oxytocin during one visit and placebo spray on an alternate visit approximately one week apart. Fifty-five minutes later maternal protective behavior toward their infant was measured in the presence of a socially intrusive stranger in a novel procedure; the enthusiastic stranger paradigm. In the oxytocin condition depressed mothers' protective response was increased. This protective response included motor and verbal behaviors to prevent the stranger approaching the infant. Interestingly, in the oxytocin condition, the proportion of time that participants visually monitored the stranger's approach to the infant compared to attending to a questionnaire or gazing around the room was reduced. Pearson's correlation between maternal protectiveness and gaze duration was $r = .66$, $p = .01$. This

seeming discrepant finding will be further discussed in the section considering future directions.

Maternal Sensitivity

In chapter 5 findings are presented exploring the sensitive caregiving of depressed mothers towards their under-one-year-old infants in two ways. Infants signal their needs to elicit adequate caregiving in numerous ways, and the percentage of time that a caregiver is attuned has been found to be a powerful predictor of infant socio-emotional development [181]. Caregivers monitor the needs of their infants using many sensory modalities but two common methods include the visual perception of an infant's facial expression and the auditory perception of the sounds an infant utters. It has been found that depressed mothers are less accurate in both these forms of interpreting the communication cues of an infant [6, 186].

We predicted that in the oxytocin condition depressed mothers would provide more sensitive care to their infant and that this effect would be moderated by the presence of a sub-optimal childhood as found in other studies [101, 102, 180]. As indicated two different outcome measures were used to explore this topic. Perceptual and

caregiving responses to pre-recorded cry sounds (the cry paradigm as described by Out et. al [175]) were collected and analysed in addition to observed, video-taped maternal sensitivity [182] during mother-infant interaction.

In the oxytocin condition mothers with a diagnosis of postnatal depression were more likely to rate an infant cry as more urgent but were also more likely to indicate that they would chose a harsh caregiving strategy in response to the crying. There was no effect of oxytocin administration on maternal sensitive interaction with their baby. The presence of a history of severe physical abuse during childhood did not moderate these findings.

Limitations and future directions

Considering the effects of intranasal oxytocin administration in a clinical cohort is important especially given findings of other researchers of the differential effects of this neuropeptide on different populations [180]. Future studies could expand upon the initial findings presented in this thesis.

One limitation of reporting separately upon subgroups of related outcome measures is that possible associations between effects

were not reported upon. In our sample of mothers, in the OT condition, there was a correlation between the quality of relationship a mother reported and how sensitive and non-intrusive she was observed to be. In the placebo condition, we found an association between how positively a mother initially described her baby and both her protectiveness and the proportion of time spent gazing towards stranger and infant when intruded upon. What is interesting is that such an association was absent in the OT condition. Given our other finding that in the OT condition mothers were more protective but spent less time gazing at their baby, it would be prudent to embark on further research on the associations between maternal representations of her infant, her sensitivity and the way in which she behaves in the enthusiastic stranger paradigm prior to using OT as a treatment in a clinical sample.

The effect of administered oxytocin upon mood needs to be further explored. It is very important to establish if our finding that oxytocin administration results in lower mood can be replicated in a larger cohort and whether this finding holds true for a general adult population with depression. Depression as a clinical construct is

likely to include many sub-sets of symptomatology and individuals [211]. Aspects of participants that future studies could measure and consider include the presence of adverse childhood experiences, premorbid personality and those with differing core symptoms in line with previous findings [92, 104, 146]. This may provide us with a clearer indication of whether particular sub-groups of depressed individuals respond better, or conversely worse to administered oxytocin.

Arguably the most important aspect of interpretation of an infant's cues, the representation a parent has of their infant or the 'Expressed Emotion' is its stability or variability over time. This thesis explored this construct at one specific moment in the mother's experience of parenting. Future studies could explore the effect of oxytocin upon perception of an infant's needs or interpretation of how difficult an infant is over time, such as how long a single administration of oxytocin sustains an improvement in parental representation. Another aspect to consider is what the effect upon the parent-infant relationship is with any change in parental representation.

The effect of oxytocin upon one aspect of executive function was also considered in this thesis. Parental sensitivity requires the parent to attend to the baby's signal, interpret the cue, then plan and carry out an appropriate response [182]. Future research could explore the effect of oxytocin on different executive function outcome measures, especially those requiring the participant to attend whilst there are competing demands, as would be common for parents in a naturalistic setting.

Given established animal literature of the role of oxytocin in maternal aggression [165], future studies could further explore this in humans, using both community and high risk samples. The 'enthusiastic stranger paradigm', developed for use in the study described in this thesis, should be used in a normative sample to establish rates of protectiveness in this setting, both in the oxytocin and placebo conditions. Alternative applications of the paradigm could be considered, such as the use of male, or potentially less trusted strangers, such as those not wearing an identifiable uniform. Other high risk samples could be considered, especially those of interest to child protection agencies, such as substance abusing

parents, parents with a psychotic illness or those with personality disorders [104]. Future studies could also attempt to better understand our finding that depressed mothers were more protective of their infant but they gazed towards their infant for a shorter duration. Further coding of 'gaze' could be developed so that perhaps gaze towards infant and stranger could be separated, although this would require sophisticated filming techniques. An attempt could also be made to rate the emotional quality of the gaze, differentiating anxious from affectionate or interested visual monitoring. Lastly, our finding may have been due to the fact that our participants were asked to complete a competing task. Future studies could design an experiment without this requirement and see whether the results replicate.

Our finding that in the oxytocin condition, depressed mothers were more likely to choose a harsh caregiving strategy in response to a pre-recorded infant cry sound is a particularly concerning result. This finding could motivate future research, replicating with larger numbers of depressed mothers, sub-classifying depressed mothers to establish if there is a differential effect such as childhood trauma to

explain this finding. In a larger sample it could be tested if the group with lower mood were more likely to use a harsh strategy or if this was a general oxytocin effect.

Finally further studies could consider the role of administered oxytocin in parental sensitivity. It would be very interesting to establish if fathers' sensitivity was enhanced in at least two contexts, those with depression in the postnatal period as well as those whose spouses are depressed [58]. Different clinical populations could be considered too, in particular those with anxiety disorders, psychotic illness, or personality disorder. Of course the effect of oxytocin on psychiatric symptom severity should also be observed/established in these groups concurrently [96].

Previous research has commented upon the effects on salience effects of administered oxytocin [104, 123, 135]. It seems that oxytocin may enhance the predominant emotional state of an individual. This idea may help to explain some of our discrepant results. Depressed mood may be worsened, a crying baby may increase the agitation and thus result in the choice of a harsher caregiving strategy and more focus may be given to how difficult a

baby is perceived to be, if the mother is already depressed, when oxytocin is administered.

In addition to various postulated pathways for intranasally administered oxytocin to result in central effects, concerns have been raised regarding the lack of standardisation between research studies with respect to intranasal administration. Guastella et. al. published guidelines on the use of intranasal administration of oxytocin after we had completed our experiment [15]. They noted that one limitation in this area of research is the capacity to control dosing and absorption. To this end they make numerous recommendations to standardize research approach to increase comparability between studies. Examples of recommendations include the exclusion of participants with septal deviation or a history of nasal congestion; reporting of details of the nasal spray formulation including its pH; the use of an enhancer; a concentrated dose and instructions to participants to ensure maximum delivery to olfactory epithelium, located in a specific area of the nasal passage [15]. These recommendations should be followed in future.

Conclusion

The current thesis provides insight into associations between oxytocin, sensitive parenting and maternal protectiveness in a cohort of mothers with a diagnosis of postnatal depression. The current findings alert us to the need for further research prior to consideration of clinical application of intranasal oxytocin administration to mothers with postnatal depression in an attempt to improve aspects of their parenting. This thesis demonstrated that there are a number of positive outcomes of using oxytocin in this clinical population. In the oxytocin condition, depressed mothers report that the quality of the relationship with their baby is better, they are more protective of their infant in the face of a socially intrusive stranger, and they rate a pre-recorded infant cry sound as more urgent. However, these findings need to be considered in concert with the negative results: In the oxytocin condition, depressed mothers report feeling sadder, they rate their babies as more difficult, and they indicate that are more likely to choose a harsh caregiving strategy in response to a pre-recorded infant cry sound.

These findings have obvious psychiatric and child protection implications. The presence of a maternal diagnosis of postnatal depression increases the risk of child abuse [7, 144]. This increased risk has been established for participants not exposed to oxytocin administration. Administration of oxytocin via the intranasal route has been found to increase salivary levels for at least seven hours [174]. We have clear ethical and moral obligations to both research participants and psychiatric patients, to conduct further research to explore the effect of oxytocin on ongoing mood and ability to parent in a non-abusive way, for a population with postnatal depression. It is clear that we would wish to avoid the iatrogenic clinical and parenting effects of worsening an already depressed mother's mood or inducing harsh parental behavior.

In conclusion this thesis provides important insights into the effects of oxytocin on parenting related outcome measures in a cohort of clinically depressed mothers. More research should be embarked upon prior to advocacy of the use of oxytocin in mothers with a diagnosis of postnatal depression.