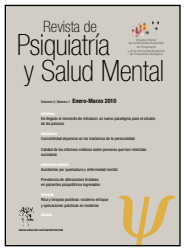
Rev Psiquiatr Salud Ment (Barc.) 2011;**4(1)**:38–41

Revista de Psiquiatría y Salud Mental

www.elsevier.es/saludmental



REVIEW

Oxytocin and autism: a hypothesis to research. Can perinatal oxitocinergic manipulation facilitate autism?

Ibone Olza Fernández,[a,*] Miguel Ángel Marín Gabriel,[b] Francisco López Sánchez,[c] Ana María Malalana Martínez[b]

[a]*Psiquiatra infantil, Servicio de Psiquiatría, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain*
[b]*Neonatólogo, Servicio de Pediatría, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain*
[c]*Obstetra, Servicio de Obstetricia y Ginecología, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain*

Received June 2, 2010; accepted October 27, 2010

KEYWORDS
Oxytocin;
Austism;
Neurobiology;
Attachment;
Bonding

Abstract The study of the neurohormonal and behavioural processes and neural mechanisms involved in the development of attachment between the infant and the mother has received increased attention over the last years. Oxytocin has been shown to play a central role in the regulation of affiliate social behaviour, including sexual behaviour, mother infant bonding and social memory and recognition. Following normal physiological vaginal birth highest levels plasmatic endogenous oxytocin are achieved, which has been related to the presence of a sensitive period which seems to facilitate bonding and initial mother and newborn attachment. Perinatal manipulation of peptidic hormones like oxytocin can have life long lasting effects on social and sexual behaviours in animal models. Disregulation of oxytocinergic system has been observed in individuals with autistic disorders. A review of the possible effects of oxytocinergic perinatal manipulation in human newborns is discussed in the present review article. The hypothesis of the possible effect of perinatal oxytocin manipulation on the ethiology of autism is discussed.

PALABRAS CLAVE
Oxitocina;
Autismo;
Neurobiología;
Apego;
Vínculo

Oxitocina y autismo: una hipótesis para investigar. ¿La alteración de la producción de oxitocina endógena en torno al parto puede estar involucrada en la etiología del autismo?

Resumen La neurobiología del apego investiga la comprensión de los procesos conductuales y los mecanismos neurales afectados en el origen y el mantenimiento del apego entre el lactante y su madre, padre y hermanos. La oxitocina desempeña un papel central en la regulación de las conductas sociales, incluidas la conducta sexual, el ape-

*Corresponding author.
E-mail: ibone.olza@salud.madrid.org (I. Olza Fernández).

1888-9891/$ - see front matter

go materno infantil y la memoria social y el reconocimiento. Los valores máximos de oxitocina endógena en las horas siguientes al parto fisiológico en el cerebro del recién nacido se han relacionado con el período sensitivo y el inicio del vínculo materno filial. La manipulación del sistema oxitocinérgico en el período perinatal puede alterar de por vida las respuestas sociales y sexuales en los modelos animales. En el presente artículo se revisan los efectos de la oxitocina endógena y exógena en el período perinatal. Se plantea la hipótesis de que la alteración del sistema oxitocinérgico podría ser uno de los posibles múltiples factores perinatales involucrados en la etiopatogenia del autismo. La alteración del sistema oxitocinérgico se puede producir mediante la administración de oxitocina sintética intraparto o la cesárea programada sin trabajo de parto previo. Se apuntan líneas futuras de investigación en esta área.

Research in the neurobiology of attachment aims to understand the behavioural processes and neural mechanisms involved in the origin and maintenance of the attachment between the infant and his/her mother, father, and siblings.

Oxytocin (OT) is a peptide formed by nine amino acids; it is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and secreted into the blood from the axonal terminations of the posterior pituitary. Its effects on uterine contractions and milk ejection have long been understood. Today we know that OT and vasopressin play a central role in the regulation of social behaviours including sexual behaviour, mother-infant attachment, and social memory and recognition.[1,2] In mammals, the mother-infant interaction and other aspects of the post-natal period can have profound effects on behaviour, and these effects may, in turn, bring about lasting changes in neuroanatomy and the neuroendocrine system.[3] OT, vasopressin, and their receptors appear to be the substrate for the transduction of early experiences to short- and long-term behavioural changes via epigenetic mechanisms in the sensitive early period.[4]

The initiation of breastfeeding, the ejection of milk, and the initiation of bonding are dependent on the pulsatile release of OT from the posterior pituitary,[5,6] among other factors, together with the synthesis of OT by myoepithelial cells via a local positive feedback mechanism.[7] Under stressful conditions, such as heavy blood loss, prolonged labour, or Caesarean section, instead of the pulsatile release there is a steady secretion of OT that reduces stimulation of the myoepithelial cells.[8,9] OT appears to be the hormone that mediates maternal behaviour in mammals. The physiological, post-partum increase of OT in the maternal brain produces a feeling of euphoria, lighter sleep, and an increased pain threshold in the mother; it also increases feelings of affection for her infant and reduces feelings of stress via a reduction in cortisol levels, among others. Levels of this hormone are increased more in women who maintain skin-to-skin contact with their infants, and they also have further elevations of OT levels in connection with periods of breastfeeding.[10] Therefore, in addition to improving post-partum uterine tone and reducing the chances of puerperal bleeding, elevation of the OT levels can facilitate mothers bonding with their infants through these processes (early skin-to-skin contact and suckling).

Endogenous OT is released in a pulsatile manner, increasing throughout the physiological birth and reaching maximum levels in the maternal brain during the first post-partum hour.[8] This phenomenon has been associated with the existence of an early, sensitive period during which a specific, neurohormonal scenario develops in both the maternal and newborn brains that is designed to facilitate the initiation of mother-infant bonding and has some characteristics similar to the imprinting observed in other species.[11,12] In elective, Caesarean births where no labour is involved, this endogenous OT peak does not occur. In experimental studies with mammals, it has been observed that females who give birth by scheduled Caesarean may be indifferent toward the newborn creature, and this has been associated with the absence of endogenous OT.[3] There is speculation that, likewise, a woman who does not undergo this increase in endogenous OT could be indifferent toward the care of her child or have more difficulty in early interactions with her infant.[3]

Various manipulations in the perinatal period may alter the physiological neurohormonal scenario in both mother and infant, and the implications of these manipulations are not well known. The OT-vasopressin equilibrium in the newborn is altered when there is an elective Caesarean, when labour is induced with synthetic OT, and when labour is stopped using oxytocin receptor antagonists such as atosiban. Likewise, mother-infant separation, bottle-feeding, and the absence of immediate skin-to-skin contact mean the disruption of endogenous OT release, and there is no in-depth knowledge of the medium- and long-term effects of these manipulations in humans.[3,13] In other mammals, in-depth studies have been conducted on the effects of perinatal manipulation of peptides in offspring, and these effects include long-term changes in social and sexual behaviour.[14] It has also been confirmed that the effects in female offspring are different from those in male offspring.[13]

Synthetic OT is utilized in a high percentage of labours, especially in nulliparas.[15] The use of synthetic OT is so extensive and widespread that there is a tendency to assume that its effects are well known and benign; there has even been a recommendation that it be used in higher doses to prevent Caesareans. However, it is believed to be the drug most commonly associated with needless and avoidable adverse effects in labour.[16]

There have been no in-depth studies of the impact of exogenous OT on behaviour or breastfeeding.[3] Exogenous OT can increase or mimic the stress response; interrupt the pulsatile release of OT and the resulting myoepithelial cell activity required to initiate lactation;[8,17] alter the signals in myoepithelial and endothelial cell OT receptors;[18] stimulate and then discharge oxytocin-secreting neurons;[19,20] and alter the OT equilibrium and the changes in neuronal architecture during the sensitive period just after birth, affecting maternal adaptation.[21,22] In summary, exogenous OT can impair the initiation of lactation by altering the pulsatile release of OT and the fluctuations in OT concentration; by desensitising the receptors; and, more speculatively, by altering infant or maternal behaviour. The intrapartum administration of OT results in a reduction of OT levels on the second day postpartum and an increase in prolactin.[23]

The assumption that perinatal manipulation with OT has no effect on the infant's behaviour has yet to be proven, but the handful of studies in animals indicate that this probably is not a valid assumption.[3] Experiments with prairie dogs have shown that manipulation of the oxytocinergic system during the perinatal period can result in life-long changes in attachment behaviours and in social behaviours, including adult pair-bonding and parental behaviours, as well as in HPA axis reactivity—findings that have been repeated in other mammals.[14]

It is commonly believed that there are two barriers that prevent OT from reaching the infant's brain: the maternal-placental barrier and the foetus's blood-brain barrier (BBB). On the one hand, there are oxytocinases in the placental barrier that appear to be effective in degrading OT. Malek et al[24] studied the maternal-fetal and fetal-maternal diffusion of OT and found that transport is greater in the maternal-to-fetal direction—in other words, synthetic OT administered to the mother may enter the fetal circulation. On the other hand, although it has always been thought that OT could not cross the BBB, important exceptions have been discovered.[25] The most important discovery is that labor represents a condition of stress for mother and infant that may result in increased cytokine release or—and this amounts to the same thing—lead to oxidative stress, which has been shown to make the BBB more permeable than usual. In addition, the infant's BBB is not so well developed as that of an adult and is possibly more permeable to small insoluble lipid molecules. In brief, it is possible that, during labor, the synthetic OT administered to the mother crosses the barriers and reaches the infant's brain.[26] In turn, various studies have shown that excess circulating OT may, by various mechanisms, desensitize OT receptors, thereby diminishing the beneficial effects derived from its activity.

In the human newborn, the earliest *attachment behaviours* are those meant to secure the mother's proximity and initiate breastfeeding (primitive neonatal reflexes),[27] as well as social interaction behaviours with the mother (described by Brazelton, NBAS). Healthy newborns have the ability to slither along the mother's abdomen and locate the mother's breast by themselves in the first two hours of life and to establish direct eye contact with the mother—behaviours that appear to be mediated by OT together with an olfactory learning.

Autism is a generalized developmental disorder characterized by three key symptoms: impairment of language and the ability to communicate; impairment of social interaction; and repetitive behaviours and restricted interests. The number of individuals diagnosed with autism has increased in recent years,[28] and the distribution by sex is four males for every five persons affected. In population studies in Denmark and California, for example, it has been observed that the cumulative incidence of autism began to increase between 1988 and 1989 and has continued to increase.[28] A major scientific controversy surrounds the increased diagnosis of autism spectrum disorders.

The possibility that exogenous, toxic environmental agents may play a causative role in autism is getting serious attention. A possible connection between autism and environmental changes during the perinatal period has been noted, though it is not clear how this connection is to be interpreted.[29-31] Breech presentation, prematurity, Caesarean delivery, and maternal age have been associated with an increased risk of autism spectrum disorders (ASD). The association of breech presentation with ASD is not thought to be causal but rather based on a common etiological factor.[30]

In the current debate on the aetiology and pathogenesis of autism, the two major aspects under discussion are the role of OT and the possible involvement of epigenetic mechanisms. Some authors have put forth the hypothesis that perinatal manipulation of OT may play a role in the genesis of autism.[32] The nature of epigenetic deregulation is as yet unknown; if it is described, however, it could explain why, so far, no one has been able to identify sequence changes in a host with candidate genes.[4,33]

The intrapartum use of synthetic OT, together with the use of epidural anaesthesia, became widespread in most countries during the 1990s, but the possibility that these two factors combined may play some role in the genesis of autism has not yet been studied. In animal experiments, the effect of synthetic OT is sexually dimorphic, and whether there are gender-dependent differences in its effect on humans is unknown. Given that there is more and more evidence that OT plays a crucial role in social interactions in humans, the possibility that intrapartum administration of OT in combination with anaesthetic drugs may be involved in the pathogenesis of autism spectrum disorders is worthy of study. The possible efficacy of OT in treating the core symptoms of autism has also begun to be studied. Intranasal synthetic OT is being used experimentally in adults with autism as a possible symptomatic treatment, with promising results.[34,35]

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Carter CS, Williams JR, Witt DM, Insel TR. Oxytocin and social bonding. Ann N Y Acad Sci. 1992;652:204-11.
2. Insel TR, Young LJ. The neurobiology of attachment. Nat Rev Neurosci. 2001;2:129-36.

3. Carter CS. Developmental consequences of oxytocin. Physiol Behav. 2003;79:383-97.
4. Gurrieri F, Neri G. Defective oxytocin function: a clue to understanding the cause of autism? BMC Med. 2009;7:63.
5. Nissen E, Lilja G, Widstrom AM, Uvnas-Moberg K. Elevation of oxytocin levels early post partum in women. Acta Obstet Gynecol Scand. 1995;74:530-3.
6. Winberg J. Mother and newborn baby: mutual regulation of physiology and behavior--a selective review. Dev Psychobiol. 2005;47:217-29.
7. Cassoni P, Marrocco T, Sapino A, Allia E, Bussolati G. Oxytocin synthesis within the normal and neoplastic breast: first evidence of a local peptide source. Int J Oncol. 2006;28:1263-8.
8. Russell JA, Douglas AJ, Ingram CD. Brain preparations for maternity--adaptive changes in behavioral and neuroendocrine systems during pregnancy and lactation. An overview. Prog Brain Res. 2001;133:1-38.
9. Dewey KG. Maternal and fetal stress are associated with impaired lactogenesis in humans. J Nutr. 2001;131:3012S-5S.
10. Matthiesen AS, Ransjo-Arvidson AB, Nissen E, Uvnas-Moberg K. Postpartum maternal oxytocin release by newborns: effects of infant hand massage and sucking. Birth. 2001;28:13-9.
11. Klaus M, Kennell J. Parent to infant bonding: setting the record straight. J Pediatr. 1983;102:575-6.
12. Bystrova K, Ivanova V, Edhborg M, Matthiesen AS, Ransjo-Arvidson AB, Mukhamedrakhimov R, et al. Early contact versus separation: effects on mother-infant interaction one year later. Birth. 2009;36:97-109.
13. Carter CS, Boone EM, Pournajafi-Nazarloo H, Bales KL. Consequences of early experiences and exposure to oxytocin and vasopressin are sexually dimorphic. Dev Neurosci. 2009; 31:332-41.
14. Henry S, Richard-Yris MA, Tordjman S, Hausberger M. Neonatal handling affects durably bonding and social development. PLoS One. 2009;4:e5216.
15. Freeman RK, Nageotte M. A protocol for use of oxytocin. Am J Obstet Gynecol. 2007;197:445-6.
16. Clark SL, Simpson KR, Knox GE, Garite TJ. Oxytocin: new perspectives on an old drug. Am J Obstet Gynecol. 2009;200:35. e1-35.e6.
17. Nissen E, Uvnas-Moberg K, Svensson K, Stock S, Widstrom AM, Winberg J. Different patterns of oxytocin, prolactin but not cortisol release during breastfeeding in women delivered by caesarean section or by the vaginal route. Early Hum Dev. 1996;45:103-18.
18. Reversi A, Cassoni P, Chini B. Oxytocin receptor signaling in myoepithelial and cancer cells. J Mammary Gland Biol Neoplasia. 2005;10:221-9.
19. Rossoni E, Feng J, Tirozzi B, Brown D, Leng G, Moos F. Emergent synchronous bursting of oxytocin neuronal network. PLoS Comput Biol. 2008;4:e1000123.
20. Febo M, Numan M, Ferris CF. Functional magnetic resonance imaging shows oxytocin activates brain regions associated with mother-pup bonding during suckling. J Neurosci. 2005;25: 11637-44.
21. Jonas W, Nissen E, Ransjo-Arvidson AB, Matthiesen AS, Uvnas-Moberg K. Influence of oxytocin or epidural analgesia on personality profile in breastfeeding women: a comparative study. Arch Womens Ment Health. 2008;11:335-45.
22. Leng G, Meddle SL, Douglas AJ. Oxytocin and the maternal brain. Curr Opin Pharmacol. 2008;8:731-4.
23. Jonas K, Johansson LM, Nissen E, Ejdeback M, Ransjo-Arvidson AB, Uvnas-Moberg K. Effects of intrapartum oxytocin administration and epidural analgesia on the concentration of plasma oxytocin and prolactin, in response to suckling during the second day postpartum. Breastfeed Med. 2009;4:71-82.
24. Malek A, Blann E, Mattison DR. Human placental transport of oxytocin. J Matern Fetal Med. 1996;5:245-55.
25. Banks WA, Kastin AJ. Bidirectional passage of peptides across the blood-brain barrier. Prog Brain Res. 1992;91:139-48.
26. Wahl RU. Could oxytocin administration during labor contribute to autism and related behavioral disorders? -- A look at the literature. Med Hypotheses. 2004;63:456-60.
27. Colson SD, Meek JH, Hawdon JM. Optimal positions for the release of primitive neonatal reflexes stimulating breastfeeding. Early Hum Dev. 2008;84:441-9.
28. McDonald ME, Paul JF. Timing of increased autistic disorder cumulative incidence. Environ Sci Technol. 2010;44:2112-8.
29. Glasson EJ, Bower C, Petterson B, De Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. Arch Gen Psychiatry. 2004;61:618-27.
30. Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics. 2009;123:1293-300.
31. Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: a review and integration of findings. Arch Pediatr Adolesc Med. 2007;161:326-33.
32. Ebstein RP, Israel S, Lerer E, Uzefovsky F, Shalev I, Gritsenko I, et al. Arginine vasopressin and oxytocin modulate human social behavior. Ann N Y Acad Sci. 2009;1167:87-102.
33. Gregory SG, Connelly JJ, Towers AJ, Johnson J, Biscocho D, Markunas CA, et al. Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. BMC Med. 2009; 7:62.
34. Bartz JA, Hollander E. Oxytocin and experimental therapeutics in autism spectrum disorders. Prog Brain Res. 2008;170: 451-62.
35. Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, Lambert TJ, et al. Intranasal Oxytocin Improves Emotion Recognition for Youth with Autism Spectrum Disorders. Biol Psychiatry. 2010;67:692-4.