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SHORT COMMUNICATION

Neonatal CSF oxytocin levels are associated with parent report of infant soothability and sociability

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Summary Oxytocin (OT) has been linked to social behavior in rodents, non-human primates, and adult humans, but almost nothing is known about brain OT activity in human newborns or its impact on social development. To better understand the role of OT biology in human social functioning, a multi-disciplinary, longitudinal study was conducted. Cerebral spinal fluid (CSF) OT levels from 18 human neonates were evaluated and examined in relationship to social-seeking behavior at term, at 3 months, and at 6 months of age. Higher neonatal CSF OT levels were consistently associated with solicitation of parental soothing and interest in social engagement with others. This is the first study to link CSF OT levels to normative human social functioning. Research is now required to test whether early OT levels serve as a biomarker for subsequent social abnormalities.
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Impairments in social functioning—observed in autism or extreme anxiety—can lead to devastating, lifelong consequences for the individual. Understanding the biology of early aberrations in infant social behavior may offer insights into, and early markers for, these developmental disorders. Oxytocin (OT) has emerged as a strong candidate in the search for the biological underpinnings of human social functioning (Meyer-Lindenberg et al., 2011).

Central OT plays a critical role in a variety of mammalian social behaviors including mother—infant attachment, affiliative contact-seeking, and social recognition (Insel, 2010). Young peer-reared rhesus monkeys display aberrant social behaviors; as a group these monkeys had lower cerebrospinal fluid (CSF) OT levels over the course of development when compared to maternally reared controls (Winslow et al., 2003). Strikingly, individual expressions of affiliative

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behaviors also correlated with CSF OT levels. While CSF OT levels are positively correlated with social functioning in this non-human primate model, this relationship is not evident in plasma OT assessments (Winslow et al., 2003), highlighting the complex regulation of central and peripheral OT systems (Amico et al., 1990; Veening and Barendregt, 2010). Finally, central OT blockade, achieved pharmacologically or genetically, results in a variety of social impairments (Carter, 2007; Insel, 2010; Meyer-Lindenberg et al., 2011; Modi and Young, 2012).

There is limited information on the role of central OT biology in adult human social functioning, primarily due to the need for invasive measurement techniques (i.e., lumbar puncture), and nothing is presently known about OT biology in human infants. We therefore capitalized on the unique opportunity to examine CSF from newborns undergoing clinical sepsis evaluation, including lumbar puncture. The vast majority (>95%) of such infants are later found not to be septic, thus allowing measurement of potential biomarkers in normal newborn CSF. Here we describe the results of a pilot study designed to measure newborn CSF OT levels in the immediate postnatal period, followed by periodic behavioral assessments during the first year of life to test for the first time the relationships between human newborn CSF OT levels and later social behavior.

1. Methods

1.1. Participants

The study was approved by the Stanford University Institutional Review Board (Protocol 10663). Eighteen neonates (12 males, 6 females) undergoing clinically indicated sepsis evaluation for standard risk factors (maternal fever, prolonged rupture of membranes, respiratory distress) were included. Exclusion criteria included known chromosomal anomalies and major malformations. With parental consent, 0.1–0.5 ml additional CSF was obtained at the time of lumbar puncture using standard sterile procedures within 72 h of birth. All subjects received 48 h of antibiotics and were found to be sepsis-negative. Gestational age ranged from 27 to 40 weeks (M = 36.14, SD = 3.80). Ethnicity and other demographics are presented in Table 1.

1.2. Fluid storage and processing procedures

CSF was transferred on ice, aliquoted, snap frozen, and stored at −80 °C. Unextracted CSF samples were assayed for OT levels (in duplicate, 100 μl per well) by enzyme immunoassay (Enzo Life Sciences, Farmingdale, NY) as previously described (Parker et al., 2010). Per Enzo Life Sciences literature, the cross-reactivity with vasopressin is 0.6% and the limit of assay sensitivity where the curve is no longer linear is ∼10 pg/ml. All samples were run on a single microplate. The intra-assay coefficient of variation was <10%.

1.3. Soothability at term or term equivalent

Prior to hospital discharge, parents were asked to review a list of soothing techniques and check which ones helped to calm their baby (e.g., talking, touching, holding, providing a pacifier, feeding, not needing to be soothed). Responses were scored categorically. Parents were blind to OT levels.

Table 1 Participant demographics and perinatal characteristics.

	Number of participants
Sex	
Females	6
Males	12
Ethnicity	
Hispanic	8
Non-Hispanic	10
Insurance status	
Public coverage	8
Private coverage	10
Gestation	
Pre-term	9
Term	9
Birth history	
Vaginal	10
C-section	8
Pitocin exposure	
Yes	7
No	11

1.4. Sociability follow-up at 3 months of age

At 3 months term-adjusted age, parents were contacted by phone to complete the Infant Behavior Questionnaire (Rothbart, 1981). Interviews were conducted in English or Spanish, as appropriate. The revised very short form of the instrument consists of 37 items assessing extroversion and positive affect, negative affect, and effortful control.

1.5. Sociability follow-up at 6 months of age

At 6 months term-adjusted age, parents were asked to return for evaluation and to complete two sets of questionnaires: (1) the IBQ and (2) the Relating to Others subscale from the Socialization section of the Vineland Adaptive Behavior Scales, 2nd ed. (Sparrow et al., 2005).

1.6. Statistical analyses

Study data were managed using REDCap and analyzed in SPSS v.19. Univariate statistical assessments were used to test relationships between CSF OT levels, perinatal factors, demographic factors, and behaviors; t-tests were used when the independent variable was dichotomous. Pearson correlations were used when the independent variable was continuous.

2. Results

2.1. CSF OT concentrations and study covariate analyses

CSF OT concentrations in newborn samples ranged from 10.25 to 34.06 pg/ml (M = 20.55, SD = 7.53). OT concentrations

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