Iulia Elena DIACONU
The Rehabilitation Hospital of Iaşi, The Neurology Clinic
Carmen Rodica ANTON,
Emil ANTON
"Gr.T. Popa" University of Medicine and Pharmacy of Iaşi
Dumitru FILIPEANU
Techical University Gh.Asachi Iasi, Romania

ANALYSIS OF POSSIBLE POSITIVE EFFECTS OF OXYTOCIN ADMINISTERED DURING BIRTH ON THE NEUROMOTOR DEVELOPMENT OF THE 0 - 5 YEAR-OLD-CHILDREN

Case Study

Keywords
Oxytocin OT,
Motor reflexes,
Psychomotor development,
Intranasal oxytocin,
Oxytocin possible positive effects,
Neuropsychiatric disorders

Abstract
Neuropeptide oxytocin (OT) receives increasing attention since, it plays a role in various behaviors including anxiety, drug addiction, learning, social recognition, empathy, pair bonding and decreased aggression. The central nucleus of the amygdala (CeA), part of the limbic system, plays an important role in learning, memory, anxiety and reinforcing mechanisms. Oxytocin receptors are found in the tissues of the cardiovascular system, reproductive system, brain, and are activated by exposure to specific stimuli. The bestknown stimuli related to reproduction are sucking, birth, cervical stimulation during sexual intercourse. Changes in the oxytocinergic system play a fundamental role in the development of autism, mental disorders, including eating disorders, obsessive-compulsive disorder, schizophrenia, with direct impact on the patient's cognition and social behavior. Some researchers have observed that intranasal Oxytocin (OT) is a potential treatment for multiple neuropsychiatric disorders. As oxytocin is a peptide, delivery by the intranasal (IN) route is the preferred method in clinical studies. Although studies have shown increased cerebrospinal

fluid oxytocin levels following intranasal administration, this does not unequivocably demonstrate that the peripherally administered oxytocin is entering the cerebrospinal fluid. For example, it has been suggested that peripheral delivery of oxytocin could lead to central release of endogenous oxytocin. It is also unknown whether the intranasal route provides for more efficient entry of the peptide into the CSF compared to the intravenous (IV) route, which requires blood–brain barrier penetration.

INTRODUCTION

Oxytocin (from the Greek word *ōkytokínē - rapid birth*) is a peptide hormone, discovered in 1952, synthesized by the paraventricular and supraoptic nuclei of the hypothalamus and stored in the neurohypophysis. This hormone is involved in multiple biological processes, but the best known are related to the reproductive function. Its peripheral effects are: contraction of the uterine smooth muscle during labor, milk ejection during lactation, regulation of the menstrual cycle, follicle luteinization in the ovary, ovarian steroidogenesis, spontaneous erection, ejaculation and orgasm (Fewtrell MS et all 2016). Other significant peripheral effects which also contribute to maintaining body health are: natriuresis, kaliuresis, lowering blood pressure, faster healing of wounds, reducing cortisol plasma concentration. Oxytocin receptors are found in the tissues of the cardiovascular system, reproductive system, brain, and are activated by exposure to specific stimuli. The bestknown stimuli related to reproduction are sucking, birth, cervical stimulation during sexual intercourse. New lines of research have revealed other important roles of oxytocin related to social behavior, OT receptors have been identified in various sites in the brain such as the cortical areas, basal ganglia, limbic system, thalamus, hypothalamus, cerebral trunk and spinal cord. In recent years, a growing number of studies have linked oxytocin to different aspects of human behavior (Kendrick, 2000; Veenema, 2012). For example, there is evidence linking the effects of oxytocin to regulating depression (Scantamburlo et al., 2007) and to social behavior, such as the aggressive one (Caldwell, Lee, Macbeth & Young, 2008; Ebstein, Knafo, Mankuta, Mestecaţi & Lai, 2012; Neumann, 2008; Pobbe, Pearson, Blanchard & Blanchard, 2012; Veenema, 2012). Other studies suggest that oxytocin is involved in sexual behavior (Meston, Levin, Sipski, Hull & Heiman, 2004), in social knowledge, in recognizing the emotional tone in verbal and non-verbal behavior, in a mother's temperament in interaction with her children and in the cooperation and competition relations in and outside the social group of cohesion. (De Dreu, 2012; Guastella & MacLeod, 2012; Strathearn, Iyengar, Fonagy & Kim, 2012; Zink & Meyer-Lindenberg, 2012). Some authors also concluded that changes in the oxytocinergic system play a fundamental role in in the development of autism, mental disorders, including eating disorders, obsessive-compulsive disorder, schizophrenia, with direct impact on the patient's cognition and social behavior (Epstein et al, 2009, 2012; Gurrieri & Neri, 2009; Higashida, Yokoyama, Kikuchi & Munesue, 2012). Other researchers have observed that intranasal or intravenous administration of oxytocin can influence social behavior (Churchland & Winkieldman, 2012; Guastella & MacLeod, 2012; Rilling et al., 2012; Singer et al., 2008) and hence the ability to recognize facial expressions (Guastella, Mitchell & Mathews, 2008; Rimmele, Hediger, Heinrichs & Klaver, 2009; Savaskan, Ehrhardt, Schulz, Walter & Scheachinger, 2008) repetitive behavior and emotions in autism (Guastella et al., 2010; Hollander et al., 2003), words with relevant meaning (Heinrichs, Meinlschmidt, Wipppich, Ehlert, & Hellhammer, 2004) and lactation (Garcia-Fortea et al., 2014).

Usually, oxytocin is used in birth to increase the frequency and intensity of uterine contractions. However, despite the growing number of studies (Guerra et al., 2011; Kurth & Haussmann, 2011; Xiong & Zhang, 2013; Brotaneck & Hodr, 1967; D'Esopo, 1964; Elert, 1966; Gonzalez-Valenzuela et al., 2014; Plothe, 2010; Sacra et al., 1969; Wells, 1965) on the impact of oxytocin administration on human behavior, there are few studies on the influence of oxytocin administration on the neuromotor development of infants between 0 and 5 years.

Next, we shall present the research hypotheses and findings on topics proposed by a number of researchers, in light of the papers published by them. Researchers Maria-Jose Gonzalez-Valenzuela, Dolores Lopez-Montiel, Ernesto Santiago Gonzalez-Mesa have analyzed, as research hypothesis, the endogenous effects of oxytocin during birth on the neuromotor development of infants at age 5. The study had two target groups of mothers: one that was administered oxytocin and the other which was not. The study was conducted in 2006, at Malaga Hospital Maternity and, out of the total of 7465 newborns, an initial group of 400 infants were selected for the study. Out of these 400, the researchers used the *Battelle Developmental Inventory* to examine the neuromotor development of a target group of 146 children. The results indicated that exposure to

synthetic oxytocin during delivery was an independent risk factor for a delay in neuromotor development. The study also revealed that administering oxytocin to mothers during birth was not influenced by the sex of the newborn or the duration of birth. Given these results and in order to prevent possible psychomotor changes, further studies are now required to analyze the effect the dose of oxytocin and the duration of the perfusion may have on the subsequent psychomotor development of children.

The used research method was that of retrospective cohort study: one cohort consisted in a group of children whose mothers were administered oxytocin to induce birth and another group of infants whose mothers were not administered oxytocin (natural or C-section birth).

The descriptive results show that, out of the 146 participants, 64 (43.8%) were not exposed to synthetic oxytocin during delivery, while the remaining 82 (56.2%) were exposed. A delay in GMD (Gross Motor Development) and FMD (Fine Motor Development) was observed in 34 (23.3%) and, respectively, 22 (15.1%) infants. The analysis considered: the mothers' age, which varied between 20 and 40 years (M¼31.5, SD¼4.28), the newborns' gestational age, which varied between 29 and 41 weeks (M¼38.17, SD¼2.42), the duration of birth that ranged from 1 to 14 hours (M¼5.85, SD¼3.39). It resulted in a table summarizing the bivariate analyses of the relations between the independent variable (exposure/no exposure to oxytocin) and control variables that could hide other risk factors (maternal age, type and length of labor, twin birth, gestational age and newborn's gender). These analyzes revealed a statistically significant association between exposure to oxytocin and the duration of birth (x2(2,146)Ľ51.60, p<.001). The goal of this retrospective cohort study was to examine whether the administration of synthetic oxytocin during labor had effects on the psychomotor development of the child at age of 5. The results of the analysis based on two variables – the duration of birth and the newborn's gender – indicate that exposure to oxytocin is an independent risk factor for a delay in the development of gross and fine motor reflexes. Specifically, when the relation between the main studied variable was adjusted by the newborn's gender, the results showed that boys exposed to oxytocin during birth incurred a risk four times higher than girls of delay in gross motor reflexes development. The potential effect of maternal age, type of birth, twin birth, newborn's gestational age in correlation with oxytocin did not show, in this study, a delay in the motor development of the child. The results of the study were also affected by the fact that 20% of the mothers in the research group were immigrants and could not be properly monitored.

The analysis of the relation between the physiology of pregnancy and lactation onset determines the assessment of the potential of correlation between the administration of oxytocin during labor and breastfeeding duration. A retrospective cohort study considered patients who had been administered synthetic oxytocin during labor induction and were considered the exposed cohort, and patients who were not administered oxytocin and represented the non-exposed cohort. Four hundred of the 7465 newborns in Malaga Maternity, in 2006, were selected randomly. Feeding information was available for 316 of these children. The potential influence or adjustment factors were analyzed by using stratified and multiple variable analyses.

Oxytocin was used during labor in a number of 189 (59.8%) newborns, multiplying the risk of bottle feeding 1.451 (95% CI 1.28-1.63). The use of oxytocin also multiplies the risk of discontinuation of breastfeeding at 3 months of 2.29 (95% CI 1.41-3.74). This effect is influenced by maternal age and is higher for mothers under 27 years. The administration of oxytocin during labor had an impact on the onset and duration of lactation, especially in cases of mothers under 27 and of babies born at term (clinical trial recorded at US NIH, ID: NCT01951040). Although some studies have shown that synthetic oxytocin administered during early puerperium can compensate for insufficient endogenous secretion under certain conditions (which contributes to the onset and maintenance of lactation), the results of this study suggest that the administration of oxytocin during labor would paradoxically have negative effects on both the onset and duration of lactation. These results indicate a possible effect of exogenous oxytocin administered during labor (to promote uterine contractions and dilatation in the stages of fetal expulsion) on both the onset and duration of lactation, and support the conception of prospective studies to confirm them. In this study, the administration of oxytocin during the first and second stage of labor had some impact on both the onset and duration of lactation, especially among mothers under 27 and in babies delivered at term.

Another goal of the research was to assess the potential influence of oxytocin administered during childbirth on the psychomotor development of children at the age of 5. This study was designed as a retrospective cohort study where children from patients who had received synthetic oxytocin during birth were considered the exposed cohort and children from patients who had not received oxytocin represented the unexposed cohort. From a total of 7465 births, in 2006, at Malaga Maternity, 400 children were randomly selected to participate in the research. A total of 148 children were assessed using the Battelle Developmental Inventory. The potential risk factors were analyzed

using the stratified analysis and the multivariate analysis (logistic regression). The use of oxytocin did not affect significantly the overall risk of developmental delay, in the study sample being RR, 1.46; 95%, confidence interval, CI [0.79-2.71]. The best analysis model of logistic regression considered the following variables: twin birth, type of birth and maternal age. In the non-instrumental vaginal birth group, administration of oxytocin increased the risk of low Battelle score, particularly when maternal age was under 28 or over 35 (odds ratio, OR, 67.14; 95% CI [5.46 -824.86]). When birth was instrumental or by caesarean section, in the case of mothers aged 28-35 years, the administration of oxytocin decreased the risk of developmental disorders (OR 0.16; 95% CI [0.04-0.66]). Although the administration of oxytocin during childbirth did not affect the overall risk of low development Battelle score, some effects were observed depending on maternal age and type of birth.

Given the growing number of multiple pregnancies and their associated problems, it remains unclear whether, in case of twin births, the chances of future health for both fetuses are equal. In this regard, it is important to note that the effects of obstetric and neonatal care beyond the perinatal period have not often been evaluated. The main concern in this situation was to analyze the impact of obstetric and perinatal variables in twin children's neuropsychological development, intelligence and school achievement. A cross-sectional and observational study was conducted on 62 pairs of 6-year-old twins, in their first year of primary education. All 124 children and their mothers were individually evaluated. A multivariate layered analysis was performed using multiple linear regressions. The type of delivery was the main variable and it showed best results in the case of vaginally spontaneously born children. By comparison, the vaginally second born male twin scored lower in nonverbal development and other areas of development, especially in births under 37 weeks. The study confirms the impact of obstetric variables on twins' academic achievement and psychological development.

OBJECTIVES

2.1. The analysis of the relation between the administered dose of oxytocin during birth and the neuromotor evolution of children between 0-5 years, based on the following variables: type of birth, maternal age;

2.2. The examination of possible positive effects of oxytocin during birth on the neuromotor development of 0 - 5-year-old children;

2.3. The analysis of the relation between the administered dose of oxytocin and role of oxytocin in social bonding, stress regulation and mental health of the child;

2.4 The analysis of the potential of oxytocin as an effective next-generation treatment therefore, the use of an OT-based pharmacotherapy to preferably jump-start the amygdala to attenuate emotional distress, including anxiety, and activate stress-coping mechanisms could be an important area for research and further our understanding of the role of the oxytocinergic system in the amygdala.

2.5 The analysis of possible correlations between the administration of oxytocin during pregnancy and the social behavior of children in the range 0-5 years.

PERSPECTIVES

We believe that the study itself will open, in relation to the intended objectives, the identification of new scientific data that will make possible a concrete assessment of the effects of oxytocin on the neuromotor development of newborns. Given the range of the proposed study, namely 0-5 years, we can identify research axioms dedicated to the prophylaxis of neuromotor development retardation. Given oxytocin's connection to such life-affirming activities as maternal behavior, lactation, selective social bonding and sexual pleasure, researchers have been working overtime to uncover its role in the brain and in regulating behavior. Preclinical and clinical evidence clearly indicates the potential of OT as an effective next-generation treatment (possibly as an *ad hoc* medication) for opioid addiction and comorbid mood disorders, as well as prevention of relapse. Oxytocin (OT) is a potential treatment for multiple neuropsychiatric disorders. As OT is a peptide, delivery by the intranasal (IN) route is the preferred method in clinical studies. Although studies have shown increased cerebrospinal fluid (CSF) OT levels following IN administration, this does not unequivocably demonstrate that the peripherally administered OT is entering the CSF. For example, it has been suggested that peripheral delivery of OT could lead to central release of endogenous OT. It is also unknown whether the IN route provides for more efficient entry of the peptide into the CSF compared to the intravenous (IV) route, which requires blood–brain barrier penetration.

CONCLUSIONS

The studies conducted so far have examined the independent effect of synthetic oxytocin administered during childbirth on the psychomotor development of children at the age of 5. Traditionally, the neurohypophyseal peptide

oxytocin (OT) is known for its effects on mediating reward, social affiliation and bonding, stress and learning and memory. There is now strong evidence that OT is a possible candidate for the treatment of drug addiction and depression-addiction co-morbidities. Oxytocin (OT) is a potential treatment for multiple neuropsychiatric disorders. As OT is a peptide, delivery by the intranasal (IN) route is the preferred method in clinical studies. Although studies have shown increased cerebrospinal fluid (CSF) OT levels following IN administration, this does not unequivocably demonstrate that the peripherally administered OT is entering the CSF. For example, it has been suggested that peripheral delivery of OT could lead to central release of endogenous OT. It is also unknown whether the IN route provides for more efficient entry of the peptide into the CSF compared to the intravenous (IV) route, which requires blood–brain barrier penetration.
We believe that oxytocin, in terms of the stage of current research, is only partially known and its potential has not yet been fully revealed.

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