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Response to Comment on “Maternal Oxytocin Triggers a Transient Inhibitory Switch in GABA Signaling in the Fetal Brain During Delivery”

Roman Tyzio, Rosa Cossart, Ilgam Khalilov, Alfonso Represa, Yehezkel Ben-Ari,* Rustem Khazipov

We tested the hypothesis that cortisol-induced release of fetal oxytocin triggers a perinatal inhibitory switch in γ -aminobutyric acid (GABA) signaling. The cortisol analog methylprednisolone did not modify GABA driving force and intracellular chloride concentration in 1-day-old rat hippocampal neurons. Together with the immaturity of the fetal rat hypothalamo-neurohypophysial system, these results suggest that oxytocin in the rat fetal brain is mainly provided by the mother.

Carbillon (1) suggests the intriguing hypothesis that during delivery, oxytocin in the fetal brain derives from the fetus itself as opposed to the mother. In particular, he proposes a model in which hypoxia-induced release of cortisol triggers release of fetal oxytocin that would drive a perinatal inhibitory switch in γ -aminobutyric acid (GABA) signaling. To test this hypothesis, we studied glucocorticoid modulation of GABA signaling in 1-day-old rats. The $GABA_A$ driving force (DF_{GABA}) was measured in CA3 pyramidal cells by using cell-attached recordings of single $GABA_A$ channels as described previously (2). In slices prepared from control rat pups, DF_{GABA} was strongly depolarizing [19.5 ± 8.3 mV (mean \pm SD); $n = 6$ cells]. In slices prepared from rat pups treated with the cortisol analog methylprednisolone (100 mg per kg of weight, intraperitoneal injection), values of DF_{GABA} were also strongly depolarizing and not significantly different from the control values (19.9 ± 7.8 mV, $n = 10$ cells, $P = 0.95$). Thus, even if a cortisol-induced release of oxytocin from the newborn rat hypothalamus were confirmed, it is insufficient to trigger the switch in the GABA action. We have also verified whether cortisol could directly affect GABA actions. In the presence of methylprednisolone (30 μ M) in the bath solution, DF_{GABA} was not different from control values (18.1 ± 6.8 mV, $n = 12$ cells, $P = 0.72$). Two-photon imaging of intracellular chloride in hippocampal pyramidal cells with chloride-sensitive fluorescent dye MQAE also failed to

reveal any change in the intracellular chloride concentration in response to methylprednisolone ($n = 247$ cells in three slices). Taken together, these findings indicate that neither the hypothesized cortisol-induced release of fetal oxytocin nor cortisol itself contribute significantly to the inhibitory switch in GABA signaling at birth, and further support the maternal origin of oxytocin in the fetal brain.

Several lines of evidence also suggest a limited contribution of the fetus to oxytocin level in the rat brain. Indeed, the hypothalamo-neurohypophysial system in the rat develops mainly postpartum [(3, 4) but also see (5, 6)]. Quantitative radioimmunoassay analysis of precursor, intermediate, and completely processed forms of oxytocin revealed that oxytocin precursors are indeed synthesized during the fetal period. However, production of fully functional amidated oxytocin starts only at term, growing steeply (without any perinatal peak) upon postnatal development (7). A more recent study with immunohistochemical and reverse transcription polymerase chain reaction analysis reported that oxytocin synthesis starts later, at postnatal (P) day 2 (3). Thus, the onset of fetal oxytocin production does not match the perinatal oxytocin-mediated changes in GABA signaling that attain half-maximum by embryonic (E) day 20 (2). It has recently been suggested (8) that it is unlikely that maternal oxytocin would reach the fetal brain because of degradation of oxytocin by placental leucine aminopeptidase, which is synthesized by syncytiotrophoblasts (9). However, administration of oxytocin to pregnant rats induced an inhibitory switch in the fetal neurons, which suggests that maternal oxytocin indeed reaches the fetal brain (2). Taken together, these results indicate that oxytocin in the fetal brain is mainly provided by the mother.

However, additional fetal contributions remain to be determined. This could be achieved by comparison of DF_{GABA} in homozygote and heterozygote fetuses of pregnant oxytocin knock-out mice.

In the human brain, the contribution of fetal oxytocin may be more substantial. Compared with altricial rats, the human brain is more advanced in development at term, including its hypothalamo-neurohypophysial system. In humans, oxytocin concentrations are higher in the umbilical artery than in the umbilical vein at term (10–13). In addition, no oxytocin was detected in either arterial or venous cord blood of anencephalic newborns (10, 12). These observations suggest that the fetus produces oxytocin at term. Moreover, although controversial (11, 12), it has been suggested that fetal oxytocin participates in parturition (10, 13, 14). What triggers the release of oxytocin in the human fetus at birth remains unknown. A common denominator might be the stress and anoxia associated with delivery or with the reduction in placental blood flow during contractions. The suggested involvement of cortisol in fetal oxytocin release during delivery is an interesting hypothesis that remains to be verified in humans. In particular, it would be of interest to determine whether glucocorticoids increase oxytocin levels in the newborn.

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Institut de Neurobiologie de la Méditerranée, Institut National de la Santé et de la Recherche Médicale U29, 163 avenue de Luminy, 13273 Marseille, France.

*To whom correspondence should be addressed. E-mail: ben-ari@inmed.univ-mrs.fr

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