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

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Tyzio *et al.* (Reports, 15 December 2006, p. 1788) reported that maternal oxytocin triggers a transient excitatory-to-inhibitory switch of γ -aminobutyric acid (GABA) signaling during labor, thus protecting the fetal rat brain from anoxic injury. However, a body of evidence supports the possibility that oxytocin is released from the fetal pituitary during delivery, not only from the mother, particularly under conditions of hypoxic stress.

Tyzio *et al.* (1) observed that in the fetal and neonatal rat hippocampus, just before delivery, there is a transient reduction in the intracellular chloride concentration and an excitatory-to-inhibitory switch of γ -aminobutyric acid (GABA) actions. The authors demonstrated that these events were triggered by oxytocin. However, one can not rule out the possibility that the oxytocin responsible from the shift in GABA signaling derives from the fetal brain, not the mother, as reported in (1).

Pro-oxytocin forms accumulate in the magnocellular neurons of fetal rats starting from embryonic day (E) 18 (2), and a surge of fully processed oxytocin was seen in pituitary glands at E21 in (2) and in other studies starting from E19 or E20 (3, 4). Two studies (3, 5) also established that the oxytocin content of fetal pituitary glands dramatically dropped during labor, which further argues in favor of a fetal pituitary release of oxytocin during this period.

Similarly, Tyzio *et al.* indicated that “maternal” oxytocin exerted a neuroprotective action on

fetal neurons during parturition. They induced anoxia and aglycemia in E21 fetuses and demonstrated that the onset of anoxic depolarization (as a marker of neuronal death) in the fetal hippocampi was significantly accelerated when the mothers or the fetuses were previously treated with oxytocin receptor antagonists. However, the fetal production of oxytocin reaches a peak precisely in E21 fetuses (2, 3), and anoxia is a possible stimulus of fetal pituitary release of oxytocin (5). Indeed, Boer *et al.* (5) showed that after decapitation of female Wistar rats at day 21 of gestation at the imminent delivery time, the oxytocin content of the fetal pituitary gland decreased by 33% in the fetuses that remained in the uterus for an additional 1.5 to 2 min in a hypoxic environment, as compared with the six fetuses in the litter that were removed first. Vasicka *et al.* (6) measured plasma oxytocin in human mothers and their fetuses and reported an excess of oxytocin in fetal samples over that found in maternal samples in 7 of 15 cases, all seven having abnormal labor, and six of the seven with fetal distress (an expression of hypoxia). These studies strongly suggest that the fetal brain is a possible source of oxytocin just before and during labor, particularly when subject to hypoxic stress.

Chen *et al.* (7) showed that acute hypoxic stress induced by a hypobaric chamber triggered an intensity- and duration-dependent in situ release of oxytocin in the median eminence of adult rats. In addition, using in vivo microinjection protocols in combination with in situ hypothalamic histologic and ultrastructural procedures, Kovacs *et al.* (8) highlighted an intrinsic tonic GABAergic mechanism that acted upon the parvocellular corticotropin-releasing hormone (CRH) neurons in vitro. They demonstrated that GABAergic cells inhibit CRH neurons and restrain the transcriptional and hormonal responses to stress. In turn, the near-term switch of GABA actions and local oxytocin release in the fetal brain may be modulated by cortisol, which is induced in humans from the fetal adrenal glands by elevated CRH concentrations currently considered as an early event regulating the cascade of events leading to parturition (9). This view is strongly supported by the findings by Chen *et al.* (7), because they observed that after bilateral adrenalectomy, the levels of oxytocin in the median eminence were decreased and there were no further significant changes in these levels when the rats were exposed to hypoxia.

Considering the clinical importance of cerebral hypoxic lesions in the fetus during labor, future research aimed at more clearly identifying fetal neurohormonal regulations during labor is needed.

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