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Neonatal allopregnanolone levels alteration: Effects on behavior and role of the hippocampus

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ABSTRACT

Several works have pointed out the importance of the neurosteroid allopregnanolone for the maturation of the central nervous system and for adult behavior. The alteration of neonatal allopregnanolone levels in the first weeks of life alters emotional adult behavior and sensory gating processes. Without ruling out brain structures, some of these behavioral alterations seem to be related to a different functioning of the hippocampus in adult age. We focus here on the different behavioral studies that have revealed the importance of neonatal allopregnanolone levels for the adult response to novel environmental stimuli, anxiety-related behaviors and processing of sensory inputs (prepulse inhibition). An increase in neonatal physiological allopregnanolone levels decreases anxiety and increases novelty responses in adult age, thus affecting the individual response to environmental cues. These effects are also accompanied by a decrease in prepulse inhibition, indicating alterations in sensory gating that have been related to that present in disorders, such as schizophrenia. Moreover, behavioral studies have shown that some of these effects are related to a different functioning of the dorsal hippocampus, as the behavioral effects (decrease in anxiety and locomotion or increase in prepulse inhibition) of intrahippocampal allopregnanolone infusions in adult age are not present in those subjects in whom neonatal allopregnanolone levels were altered. Recent data indicated that this hippocampal involvement may be related to alterations in the expression of gamma-aminobutyric-acid receptors containing α4 and δ subunits, molecular alterations that can persist into adult age and that can, in part, explain the reported behavioral disturbances.

Contents

Abbreviations: AlloP, allopregnanolone; KCC2, cotransporter K^+–Cl^- 2; DHEA, dehydroepiandrosterone; EMS, early maternal separation; GABA, gamma amino-butyric acid; NMDA, glutamate N-methyl-D-aspartate; MAP2, microtubule-associated protein 2; PN, postnatal day; PPI, prepulse inhibition; THDOC, tetrahydrodeoxycorticosterone; $GABA_AR$, type A gamma amino-butyric acid receptors.

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1. Introduction

Allopregnanolone (AlloP) or 3α-hydroxy-5α-pregnane-20-one is a 3α-reduced progesterone metabolite (Baulieu, 1998; Robel and Baulieu, 1994; Rupprecht, 2003) that acts as positive allosteric modulator of the type A gamma amino-butyric acid receptors ($GABA_AR$) (Farrant and Nusser, 2005; Hosie et al., 2006; Majewska et al., 1986; Puia et al., 1990, 1991). Previous works have shown the importance of endogenous AlloP levels during development for adolescent and adult behavior and for nervous system maturation. It has been demonstrated that the inhibiting the formation of 5α-reduced steroids during late gestation in rats reduces gestational length, the number of viable pups per litter, and impairs cognitive (object recognition task) and neuroendocrine function (corticosterone levels) in the juvenile offspring (Paris et al., 2011a,b). Moreover, rat cortical levels of AlloP in the forebrain of embryonic rats vary widely throughout development. During the last pregnancy period AlloP levels sharply increase, and decline prior to parturition (Grobin and Morrow, 2001). These high AlloP levels during pregnancy could be part of a protective mechanism against gestational stress, as it has been described that the central opioid inhibition of neuroendocrine stress responses in pregnancy in the rat is induced by the neurosteroid AlloP (Brunton et al., 2009). From the day of birth and during the two first weeks of life, cortical AlloP levels show important fluctuations, as indicated by an initial elevation on the day of birth and a progressive decrease in the first week, followed by a secondary elevation during the second week, reaching maximum values between postnatal days (PN) 10–14 (Grobin and Morrow, 2001; Grobin et al., 2003). Moreover, AlloP levels show sexual dimorphism at PN25. Female cerebral cortical AlloP levels at 21–33 days following birth are higher than males (Grobin and Morrow, 2001).

Although GABA is the main inhibitory neurotransmitter in the mammalian adult encephalon, it exerts excitatory actions in several brain structures during early development (Ben-Ari et al., 1994, 1997; Obrietan and Van den Pol, 1995; Owens and Kriegstein, 2002). Interestingly, the secondary peak in AlloP levels is coincident with the period of transition from excitation to inhibition in the function of $GABA_AR$ (Grobin and Morrow, 2001; Staley et al., 1995). The presence of this AlloP peak coinciding with this important change in GABA signaling suggests that GABAergic neurosteroids may participate in the development of GABAergic neurotransmission. GABA may have a major role in brain maturation, since in immature cells GABA participates critically in the formation of synapses and activity in neuronal networks (Ben-Ari et al., 2007). It is possible that the elevation in cortical AlloP levels influences the function of $GABA_AR$ during the second week of life, and the timing of increased AlloP levels may differentially impact particular brain regions (Grobin and Morrow, 2001), including the hippocampus (Mellon, 2007). Thus, variations in the maturation of GABA neurotransmission in several brain regions can influence adult behaviors that are mediated or related to this neurotransmitter and to these brain regions.

In this article, we review the main published data related to the effects of neonatal AlloP levels alteration on adult and adolescent behavior, and the role that the hippocampal GABAergic system plays in these effects (see Fig. 1 for the summary diagram).

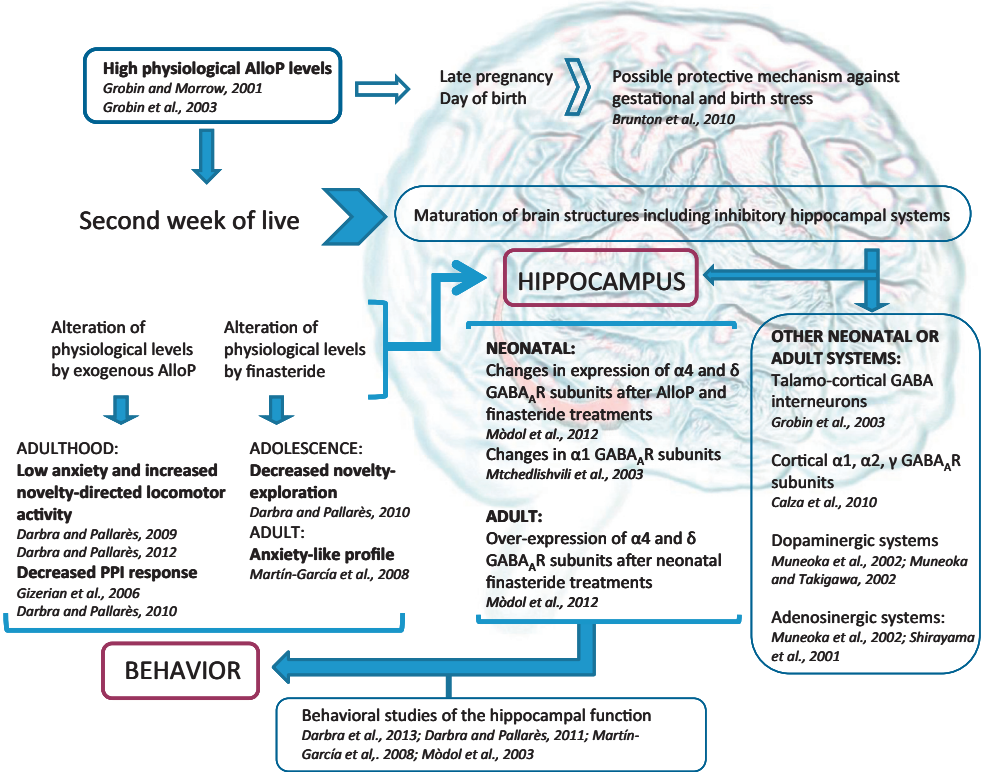

Fig. 1. Summary diagram indicating the most studied relationships between neonatal AlloP, adult behavior and hippocampal GABAergic systems.