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Revisiting the roles of progesterone and allopregnanolone in the nervous system: Resurgence of the progesterone receptors

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ABSTRACT

Progesterone is commonly considered as a female reproductive hormone and is well-known for its role in pregnancy. It is less well appreciated that progesterone and its metabolite allopregnanolone are also male hormones, as they are produced in both sexes by the adrenal glands. In addition, they are synthesized within the nervous system. Progesterone and allopregnanolone are associated with adaptation to stress, and increased production of progesterone within the brain may be part of the response of neural cells to injury. Progesterone receptors (PR) are widely distributed throughout the brain, but their study has been mainly limited to the hypothalamus and reproductive functions, and the extra-hypothalamic receptors have been neglected. This lack of information about brain functions of PR is unexpected, as the protective and trophic effects of progesterone are much investigated, and as the therapeutic potential of progesterone as a neuroprotective and promyelinating agent is currently being assessed in clinical trials. The little attention devoted to the brain functions of PR may relate to the widely accepted assumption that non-reproductive actions of progesterone may be mainly mediated by allopregnanolone, which does not bind to PR, but acts as a potent positive modulator of γ-aminobutyric acid type A ($GABA_A$) receptors. The aim of this review is to critically discuss effects of progesterone on the nervous system via PR, and of allopregnanolone via its modulation of $GABA_A$ receptors, with main focus on the brain.

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Abbreviations: ACTH, adrenocorticotropic hormone; AD, Alzheimer's disease; CNS, central nervous system; 5α-DHP, 5α-dihydroprogesterone; EAE, experimental autoimmune encephalomyelitis; $GABA_A$ receptors, γ-aminobutyric acid type A receptors; GC/MS, gas chromatography/mass spectrometry; HRT, hormone replacement therapy; 3α-HSD, 3α-hydroxysteroid dehydrogenase; 3β-HSD, 3β-hydroxysteroid dehydrogenase; LPC, lysophosphatidylcholine; MBP, myelin basic protein; MCAO, middle cerebral artery occlusion; mPR, membrane progesterone receptors; nM, nanomolar; NP-C, Niemann-Pick type C disease; OPC, oligodendrocyte progenitor cell; P0, peripheral myelin protein zero; PMP22, peripheral myelin protein-22; PNS, peripheral nervous system; PR, progesterone receptors; PR-A, progesterone receptor isoform A; PR-B, progesterone receptor isoform B; PRE, progesterone response element; RIA, radioimmunoassay; SRC-1, 2, 3, steroid receptor coactivator-1,2,3; Src kinases, proto-oncogene tyrosine-protein kinases; TBI, traumatic brain injury; VMN, ventromedial nuclei of the hypothalamus; VTA, ventral tegmental area.

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1. Introduction: historical background

The brain is a major target of progesterone, and the hypothalamus was the first region where progesterone receptors (PR) were localized. In the early 1970s, the uptake of tritium ([^{3}H])-labeled progesterone by the nuclei of hypothalamic neurons was demonstrated by autoradiography in the guinea pig, suggesting a direct action of the hormone on neural cells. Moreover, pretreating the animals with estradiol was shown to enhance the nuclear uptake of radioactivity (Sar and Stumpf, 1973). At this time, it was already known that both hypothalamus and pituitary gland are targets for the ovulation-blocking actions of progestogens (Kanematsu and Sawyer, 1965). However, the study of brain PR remained elusive at the beginning, as binding of natural progesterone to its receptors was found labile, thus precluding the use of standard binding techniques. This changed with the advent of [^{3}H]promegestone (R5020), a highly potent synthetic 19-norpregnane derivative. Promegestone indeed binds to PR with high selectivity and affinity, allowing the characterization of PR binding in progesterone target tissues in relation to biological responses (Raynaud and Ojasoo, 1984). Within the rat hypothalamus, binding studies with [^{3}H]promegestone demonstrated estradiol-inducible PR, and it was shown that their upregulation is necessary for the activation of female reproductive behavior (Blaustein and Wade, 1978; MacLusky and McEwen, 1978; Moguilewsky and Raynaud, 1977, 1979b; Parsons et al., 1980).

The early binding studies also revealed that within the brain, PR expression is not limited to the hypothalamus, but that they are widely distributed throughout the brain and present in both cerebral cortex and subcortical regions. However, much lower levels of PR were found outside the hypothalamus, and they were not inducible by estrogen within many regions (MacLusky and McEwen, 1978; Parsons et al., 1982). Moreover, PR are also difficult to detect by immunohistochemistry at the light microscopic level in extra-hypothalamic regions of the adult rodent brain (Lopez and Wagner, 2009; Quadros et al., 2007, 2008; Warembourg et al., 1986). There may be two main reasons for the difficulty in studying PR outside the hypothalamus. First, PR are strongly induced within hypothalamic neurons by estrogen treatment, but only modestly or not at all in other brain regions. Second, whereas hypothalamic PR show a strong nuclear localization, allowing their easy detection, PR in neurons outside the hypothalamus are also located in extra-nuclear sites, as demonstrated recently by immunoelectron microscopy. This study indeed revealed abundant PR labeling within axons, dendrites and at the level of synapses (Waters et al., 2008). Already an earlier study using conventional immunohistochemistry had reported the presence of both PR and estrogen receptors in dendrites and axon terminals (Blaustein et al., 1992). These findings are consistent with expression studies showing elevated expression of PR mRNA outside the hypothalamus (Guerra-Araiza et al., 2001, 2003; Hagihara et al., 1992; Intlekofer and Petersen, 2011; see also the nuclear receptor expression websites NURSA and MousePat). Obviously, in neuronal compartments far distant from the nucleus, PR would not be expected to act as transcription factors, but they could instead influence neurotransmission, possibly by interacting with membrane proteins (see Section 4). It is interesting to note that a subcellular distribution in axons and dendrites has also been reported for the androgen receptor in neurons outside the hypothalamus. It was moreover shown that the cerebral cortex, and not the hypothalamic and limbic nuclei involved in the control of reproductive functions, contains the highest density of androgen receptor expressing cells (Doncarlos et al., 2003, 2006).

In this review, the term "progesterone receptors" and the abbreviation PR refer to the so-called "classical" intracellular receptors, without distinction between the two isoforms PR-A and PR-B, which are both transcribed from a single gene and also expressed in the brain (see Section 5). The term PR does not include here the multiple membrane receptors of progesterone, which have been identified more recently. Their biological significance is indeed beyond the scope of this review and has been extensively discussed elsewhere (Brinton et al., 2008; Peluso et al., 2012; Thomas, 2008; Thomas and Pang, 2012; Wendler et al., 2012).

Since the demonstration of PR in the brain, research has largely focused on the reproductive functions of hypothalamic PR, and the extra-hypothalamic receptors have largely remained unexplored (Levine et al., 2001; Mani and Portillo, 2010; Mani et al., 1994). Only a few studies have raised the possibility that brain PR outside the hypothalamus may play a wider role in the regulation of neuron activity and brain functions extending beyond reproduction (Ghoumari et al., 2003; Waters et al., 2008; Woolley and McEwen, 1993; Wu et al., 2006). However, within the spinal cord and peripheral nerves, PR have previously been proposed to play an important role in neuroprotective and regenerative mechanisms (Chan et al., 2000; Koenig et al., 1995; Labombarda et al., 2003).

The lack of interest in the functional significance of PR outside the hypothalamus, in spite of the multiple effects which progesterone exerts in the brain, cannot only be explained by their apparently lower abundance. A main reason may be that concomitantly to studies on the reproductive functions of hypothalamic PR, there has been an important line of research concerning the anesthetic, anxiolytic, analgesic and anticonvulsant actions of progesterone, which are mainly mediated by its neuroactive metabolite allopregnanolone. All started in the early forties, when Hans Seyle reported that high doses of progesterone and some of its metabolites induce anesthesia in rats (Seyle, 1941, 1942). This observation was the demonstration that steroids can very rapidly modulate brain excitability, and it led to the development of water-soluble synthetic steroidal anesthetics, which were clinically used during the seventies. For their design, attention was focused on metabolites of progesterone which were more potent than progesterone itself (Gyermek and Soyka, 1975). A therapeutically efficient mixture with the brand name Althesin was composed of alphaxolone (3α-hydroxy-5α-pregnane-11,20-dione), a synthetic derivative of the natural progesterone