Maturitas 62 (2009) 349–355

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Progestogens and brain: An update

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ARTICLE INFO

Article history:
Received 6 August 2008
Received in revised form
15 November 2008
Accepted 18 November 2008

Keywords:
Progesterone
Progestogens
Brain
Allopregnanolone
Beta-endorphin

ABSTRACT

Each synthetic progestins has its own specific activities on different tissues, which can vary significantly between progestins of different classes and even within the same class. Indeed, different progestins may support or oppose the effects of estrogen depending on the tissue, thereby supporting the concept that the clinical selection of progestins for HRT is critical in determining potential positive or detrimental effects. These actions might be particularly relevant in the central nervous system (CNS) where progesterone (P) has pivotal roles besides reproduction and sexual behavior, going from neuropsychological effects to neuroprotective functions. Growing evidence supports the idea that synthetic progestins differ significantly in their brain effects, and clinical studies indicate that these differences also occur in women. Molecular and cellular characterization of the signaling properties of synthetic progestins in brain cells is therefore required and is hoped will lead to a better clinical utilization of the available compounds, as well as to new concepts in the engineering of new molecules. The aim of the present paper is to briefly review and compare neuroendocrine effects of progestogens with special reference to P metabolism into neuroactive steroids and the opioids system.

Contents

1. Introduction

Several epidemiological and observational studies have investigated the role of hormone replacement therapy (HRT) in postmenopausal women. Within a few years, clinicians shifted from considering HRT as the panacea for everything to considering it a venomous poison with which women, in search of the fountain of eternal youth, could instead harm themselves. This debate is not yet settled and the unexplained discrepancy between basic science and some of the clinical trials has fueled the discussion. One of the hottest areas of discussion remains the role of progestins. For many years, progestins were considered only as necessary additions to estrogen to protect the endometrium. However, we now know that every progestin has its own specific activities on different tissues, which can vary significantly between progestins of different classes and even within the same class. Indeed, different progestins may support or oppose the effects of estrogen depending on the tissue, thereby supporting the concept that the clinical selection of progestins for HRT is critical in determining potential positive or detrimental effects. These actions might be particularly relevant

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doi:10.1016/j.maturitas.2008.11.023

in the central nervous system (CNS) where progesterone (P) has pivotal roles besides reproduction and sexual behavior, going from neuropsychological effects to neuroprotective functions. The aim of the present paper is to briefly review and compare neuroendocrine effects of progestogens with special reference to P metabolism into neuroactive steroids and the opioids system.

2. Mechanisms of action of progesterone in the CNS

A comprehensive account of the molecular and cellular activities of P on the CNS is beyond the scope of this article, and several recent reviews of the area are available [1,2]. However, in the attempt to describe the biological plausibility for the hypotheses that P and progestins greatly affect aspects of cognitive function, the mechanisms that seem most relevant will be briefly described here.

The different physiological effects of P can be mediated by both nuclear receptors (PRs) and membrane receptors [3].

The most common isoforms of PRs are PR-A and PR-B, which are responsible for the transcriptional effects of P. Although both PRs are generated from a single gene [4], PR-B differ from PR-A by an additional 164 amino acid sequence in the N-terminal region [5], thus the different structure give them diverse transactivational properties observed both in vitro [6,7] and in vivo [8,9]. Interestingly, a third isoform, PR-C, has also been identified, which is thought to modulate the transcriptional activity of PR-A and PR-B [10,11]. The differential structure of the PR isoforms confers distinct tissue-specific responses to P, through post-translational modifications, dimerization and recruitment of cofactor proteins contributing to the differential transactivation properties of each isoform, and leading to the regulation of distinct substrates of P-dependent target genes [2].

In the CNS, PR-A and PR-B were identified, although their biological properties are not yet completely defined [12–14]; instead, there is no evidence for the existence of PR-C isoform to date [2]. Reverse transcription-polymerase chain reaction (RT-PCR) analyses revealed the expression of both the PR-A and PR-B mRNA transcripts in all regions of the brain where the neural PRs are known to be present [2]. Their co-localization in several brain districts such as amygdala, hippocampus, cortex, basal forebrain, cerebellum, locus coeruleus, midbrain rafe nuclei, glial cells and grey matter could confirm the involvement of P in the control of well-being, cognitive functions and memory processes in physiological as well as pathological conditions [15]. Furthermore, in the adult female rat brain, E2 and P differentially regulate the isoforms in distinct regions of the brain [16]. In the hypothalamus, estrogen can up-regulate PR-A and B expression since PRs are expressed in the same areas of the estrogen receptors, while P itself down-regulate them. In the hippocampus only PR-A expression is up-regulated by E2, while P has not got any influence in both PR expression [16]. On the other hand, in the cerebellum and the frontal cortex, neither E2 nor P has any effect on PR isoforms mRNA expression. Moreover, the transcription of PR isoform varies with the esotrous cycle in a region-specific manner; for example, studies on E2-treated rhesus macaques indicate a region-specific regulation of the PR isoforms, with PR-B expression being predominant in the hypothalamus and PR-A in the pituitary [17,18].

The increasing in vitro and in vivo evidence of differential transcriptional activities and co-regulator interactions between PR-A and PR-B, predict that these two isoforms could have distinct roles in mediating additional and/or alternate signaling pathways within steroid sensitive neurons [2]. In addition, genetic variations of the common progesterone receptor gene described in the endometrium and in the breast tissue, might be associated with functional differences inside the brain. Similarly, the methylation status of the PR-A and PR-B promoter regions is well-documented to be associated with receptor transcriptional silencing and hypermethylation of PR-B induces a down-regulation of the receptor [19]. However, no data is currently available for methylation status of brain PR-A and PR-B. In ongoing clinical trials, premature infants have been treated with a continuous infusion of P and estradiol for the initial few weeks of life: premature infants treated with hormones achieved normal psychomotor development earlier than untreated premature infants [20]. Whereas this suggests some beneficial effects of hormonal treatment, the long-term consequences of this relatively new practice are not completely understood.

Concerning non-classical pathways, several studies have demonstrated that P is able to interact with membrane receptors such as the P receptor membrane component 1 (PGRMC1), sigma 1 receptor and GABA-A receptor, through its neurometabolite allopregnanolone (AP); PGRMC1 is localized on the membrane of hypothalamic and spinal neurons [21,22] and its expression was shown to be induced by E2 treatment, suggesting a role in the activation of female sex behavior [21]. Moreover, a role of PGRMC1 in mediating protective effects of P in the nervous system is also supported by the observation that its mRNA and protein were up-regulated by P treatment in dorsal horn neurons of spinal cord-injured male rats [22]. Another membrane receptor of P is the sigma 1 receptor that is involved in the neuronal aging processes [23,24]. Sigma 1 receptor is involved in the potentiation of the NMDA response of hippocampal neurons and the NMDA-evoked norepinephrine release but the presence of P lead to a reduction of sigma one activity [25,26].

Furthermore, P plays a role in the control of other transmission systems like opioidergic, serotoninergic and cholinergic. The nicotinic receptor of acetylcholine is a target of P as well and P inhibit the activity of the receptor independently of the membrane potential [27,28].

Studies in vitro have shown that PR, like other steroid receptors, ca be modulated by compounds other than steroids in a "ligand-independent manner". These molecules includes cyclic nucleotides that increase intracellular kinase activity [29], as well as extracellular compounds that interact with membrane receptors and stimulate intracellular phosphorylation pathways, including growth factors and neurotransmitters like dopamine.

Thus, the "ligand dependent" (genomical/classical and non-genomical/non-classical) and the ligand-independent mechanisms of PRs activation and sensitization let steroids to widely affect the regulation of cerebral activities.

3. Neuroprotective effects of progesterone

P exerts important neuroprotective and neurotrophic actions especially in those neuronal populations most vulnerable to excitotoxic and ischemic damages such as pyramidal cell in the hippocampus and in the cortex, purkinje cells and mesencefalic dopaminergic cells [30,31].

In fact, several experimental models have been reported data about the neuroprotective effects of P in reducing neuronal vulnerability to neurotoxic molecules [32], the loss of cells after ischemic episodes [33] and inhibiting lipid peroxidation, the generation of isoprostanes [34] and the expression of pro-inflammatory genes [35]. Beneficial effects of P have been documented in models of traumatic brain injury (TBI) in rats and in clinical experience [36].

Edema, secondary excitotoxic neuronal death in the vicinity of the lesion and the retrograde neuronal degeneration are consequences of TBI. Treatment with P reduced both edema and secondary neuronal losses and improved behavioral recovery after TBI in both sexes. Moreover, in female rats, protected by their endogenous P levels, the water content after TBI was lower than males [37,38]. Probably the role of P in reducing edema can be explained by its interaction with aquaporine 4, a membrane protein involved in water homeostasis The administration of progesterone