REVIEW

Progesterone Inhibitory Role on Gastrointestinal Motility

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Summary

Progesterone is a steroidal hormone that is produced from the corpus luteum of the ovaries and from the placenta. The main function of progesterone is to promote the secretory differentiation in the endometrium of the uterus and to maintain pregnancy by inhibiting uterine contractions throughout pregnancy. Progesterone performs its actions by activating the classical progesterone nuclear receptors that affect gene transcription and by the non-classical activation of cell surface membrane receptors that accounts for the rapid actions of progesterone. Besides the reproductive roles of progesterone, it exerts functions in many tissues and systems such as the nervous system, the bone, the vascular system, and the gastrointestinal (GI) tract. This review will summarize the recent literature that investigated the role of progesterone in GI tract motility. Most literature indicates that progesterone exerts an inhibitory role on gut smooth muscle cells in part by elevating nitric oxide synthesis, which induces relaxation in smooth muscle. Moreover, progesterone inhibits the signaling pathways that lead to contraction such as Rho kinase inhibition. These data serve as a quick resource for the future directions of progesterone research that could lead to better understanding and more effective treatment of gender-related GI tract motility disorders.

Key words

Progesterone • Smooth muscle • GI tract

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Introduction

Progesterone is the natural progestin that is mainly produced in the corpus luteum of the ovaries and by the placenta. It is synthesized from the cholesterol derivative, pregnenolone by the actions of the cholesterol side-chain cleavage enzyme and 3-beta-hydroxysteroid dehydrogenase [1,2]. Although the focus of progesterone and its applications have been associated with female physiology, it is present in male gonads and regulates several male physiological and pathological functions such as spermiogenesis and androgen synthesis [2,3]. Moreover, progesterone is produced in the male and female central nervous systems (CNS) and all the required enzymes and precursors for progesterone synthesis are present in CNS where it acts directly on neuronal tissues [4]. Furthermore, Progesterone exerts several important functions in tissues other than the reproductive tissue such as the cardiovascular, renal, adipose, bone, and gastrointestinal tissues [3,5]. The aim of this review is to summarize the role of progesterone in gastrointestinal (GI) tract motility function and to highlight the potential therapeutic benefits and risks of progestin preparations in the GI tract.

Mechanism of progesterone actions

Progesterone produces its physiological functions by activating classical and non-classical signaling pathways [6]. In the predominant classical

pathway, progesterone binds to its receptor; a member of the nuclear receptor superfamily of transcription factors [6]. There are two main isoforms of progesterone receptors (PRs), PR-A and PR-B. Binding of progesterone to PR induces its translocation to the nucleus where the complex binds to progesterone response elements and initiates or prevents the transcription of a wide array of proteins [7]. However, the non-classical pathway produces rapid actions by activating cell surface receptors that resemble G protein-coupled receptors [8]. Progestin binding to these receptors rapidly activates various intracellular signaling molecules such as elevation of intracellular calcium, extracellular signal-regulated kinases 1 / 2 (ERK1/2), mitogen-activated protein kinase (MAP) kinase and Protein kinase B/phosphatidylinositol 3-kinases (Akt/PI3K) (Fig. 1) [9].

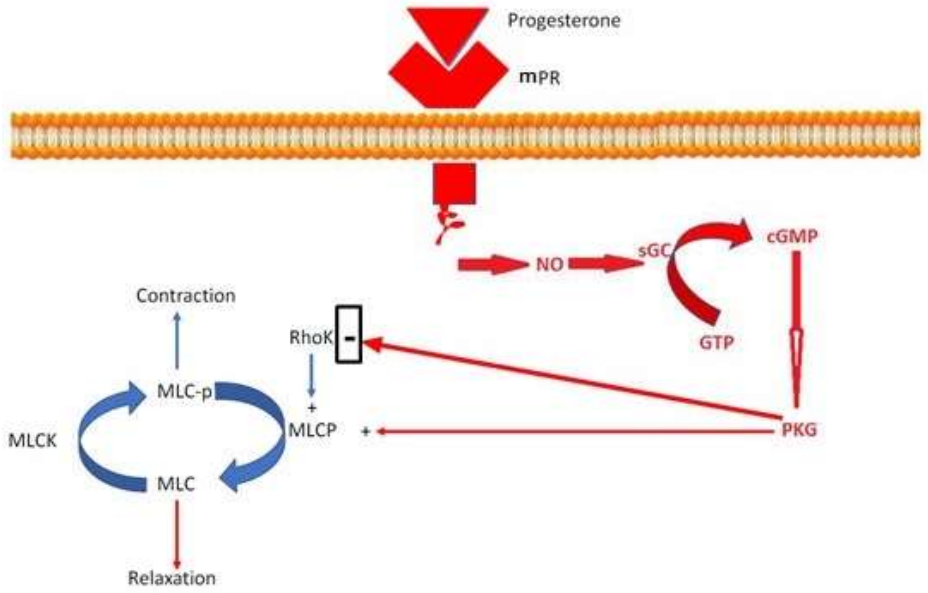

Fig. 1. Progesterone mechanism of action. The classical pathway involves the nuclear progesterone receptor (nPR) dimerization and translocation to the nucleus to induce genomic effects *via* activating or inhibiting gene transcription. The non-classical pathway is rapid action that involves membrane progesterone receptor (mPR) and the subsequent activation of several second messengers such as elevation of intracellular calcium (Ca^{2+}), extracellular signal-regulated kinases (ERK) and Protein kinase B (AKT)

Functions of progesterone

The main reproductive function of progesterone is to promote the secretory differentiation in the endometrium of the uterus during the second half of the female sexual cycle [10]. These changes aim to prepare the uterus for implantation of the fertilized ovum [10]. In addition to this effect on the endometrium, progesterone decreases uterine contraction force and frequency to prevent the explosion of the newly implanted ovum and maintains a quiescent environment for fetal development [11]. Additionally, it influences the activity of the intrauterine immune system through the regulation of inflammatory mediators' production from T cells. This action of progesterone helps to maintain pregnancy as well by increasing the immunological protection against any potential microbial threats [12]. Moreover, progesterone prepares the breasts for lactation through its action to promote proliferation and enlargement of alveolar cells of the breast [13].

In addition to the unquestionable role of progesterone in reproduction, it has numerous functions in various organs in the body. In the central nervous system, progesterone is produced at high concentrations from glial and neuronal cells [14]. Progestins produced in the CNS are called neurosteroids. They modulate many neuronal functions either by upregulating or downregulating neurotransmissions and are involved in cognition, memory, neuroprotection, and myelination processes [14]. Moreover, progesterone is involved in sexual and maternal behaviors [15,16]. Like in the reproductive system, neurosteroids act through classical and non-classical pathways in the CNS [17].

Progesterone plays an essential role in bone physiology; it stimulates bone formation and slows down resorption. However, its effect is influenced by estrogen, age, and the predominant signaling pathways [18].

Progesterone has been studied in association with diabetes and gestational diabetes. It inhibits glucose uptake and increases liver gluconeogenesis [19]. Progesterone mediates this effect by acting on progesterone receptor membrane component 1 in the liver

that could exacerbate hyperglycemia in diabetes [19]. Conversely, progesterone improves neuronal glucose metabolism through the augmentation of different glucose transporters in neuronal cells [20]. The latter effect may be responsible for the neuroprotective role of progesterone.

The primary effects of progesterone on myometrial smooth muscle cells' contractility suggest that it may exert similar actions on smooth muscle cells of other tissues. PRs are present in vascular smooth muscle cells and progesterone administration in humans lowers blood pressure and inhibits angiotensin II-induced contraction in vascular muscle cells [21,22]. The relaxation effect of progesterone on vascular smooth muscle is independent of vascular endothelium and triggered directly via activation of PRs present in smooth muscle cells [23]. The effects of progesterone on vascular smooth muscle cells' tone involve several actions on different signaling pathways that lead to smooth muscle relaxation. One prevalent mechanism is the activation of non-classical progesterone cell surface receptors that in turn activate an inhibitory G protein and subsequently activation of several intracellular pathways that upregulate nitric oxide intracellular levels which leads to inhibition of vascular smooth muscle contraction [24]. Another pathway that is responsible for the inhibitory effect of progesterone on vascular smooth muscle cells contraction is the activation of the cyclic adenosine monophosphate (cAMP) pathway which inhibits contraction by reducing myosin light chain-20 (MLC 20) phosphorylation by activating progesterone cell surface receptors directly and involving the MAP kinase/ERK-, Akt/PI3K signaling activation [23]. Moreover, progesterone induces vascular smooth muscle relaxation by reducing intracellular calcium levels through activation of membrane progesterone receptor alpha (mPRα)-dependent signaling pathways, specifically, MAP and Akt signaling [25].

Similarly, progesterone targets the smooth muscle of the gastrointestinal tract and affects the contractile apparatus there. The remainder of this review will summarize the recent advances in the role of progesterone in gastrointestinal tract contraction relaxation pathways.

Progesterone in Gastrointestinal tract motility

Gastrointestinal tract motility is altered during pregnancy as a result of plasma hormonal changes such as progesterone levels. Progesterone affects gastrointestinal motility where it enhances gastric emptying at high doses as those seen toward the end of pregnancy [26]. Smooth muscle cells from the colon of women with intractable constipation and slow transit time were studied by Zuo-Liang Xiao *et al.* to elucidate the role of progesterone in constipation. They found that smooth muscle cells from women with constipation exhibited lower contraction compared to control samples. Moreover, PRs were overexpressed in smooth muscle cells from constipation women and there was downregulation of Gαq/11 and up-regulation of Gαs, responsible for contraction and relaxation respectively [27]. Moreover, progesterone could increase gastric sensitivity to inhibitory gut neurotransmitters such as calcitonin gene-related peptide (CGRP) by enhancing CGRP receptors in gastric tissue. This effect is correlated with the levels of CGRP during pregnancy and could account in addition to the reported disturbed gut motility to the increased gut irritability as CGRP is one of the main sensory neurotransmitters in the gut [28]. *In vitro*, progesterone inhibited the resting tension of the fundus and body longitudinal muscle strips, and it inhibited the mean contractile amplitude of body and antrum longitudinal and circular muscles [29]. The effect of progesterone was mostly a direct effect on gastric smooth muscle as inhibitors of other mediated pathways did not influence the effect of progesterone on gastric motility [29].

From another point of view, progesterone decreased gastrointestinal tract inflammatory cytokines such as IL-1β and tumor necrosis factor-alpha. Which helps to protect the gut structure and prevents apoptosis after gut inflammation [30]. This observation suggests the potential use of synthetic progesterone in such situations, especially if they are accompanied by diarrhea as these inflammatory cytokines are known to enhance gut motility [31, 32]. Moreover, progesterone provides neuroprotective and anti-inflammatory effects on the enteric nervous system in Parkinson's disease (PD) mice model and thus could ameliorate the associated gut motility disturbances in PD. This observation could explain the beneficial effect of female hormones in PD susceptibility [33]. However, these effects of progesterone on gut motility are indirect effects through the enteric nervous system.

Recently, the role of progesterone in gastric smooth muscle motility was investigated in more detail by Al-Shboul and co-authors [34-36]. Single smooth muscle cells from rat gastric tissue were used to investigate

the role of progesterone in gastric motility. Both isoforms of progesterone receptors (PR), PR-A and PR-B are present in gastric smooth muscle cells suggesting a direct site of action of progesterone [35]. Preincubation of the dispersed smooth muscle cells 10 minutes before the administration of acetylcholine (Ach), inhibited the induced contraction by acetylcholine. Moreover, progesterone preincubation inhibited Ach-induced Rho kinase II activity without affecting its expression level suggesting that progesterone acts rapidly and directly of gastric smooth muscle cells to inhibit the contractile activity [34]. The same group showed that the effect of progesterone on Ach-induced contraction was achieved by the production of nitric oxide (NO] by progesterone from smooth muscle cells. Nitric oxide in turn induces the formation of cyclic guanosine monophosphate (cGMP) that activates protein kinase A (PKG) that plays a key role in smooth muscle relaxation [35].

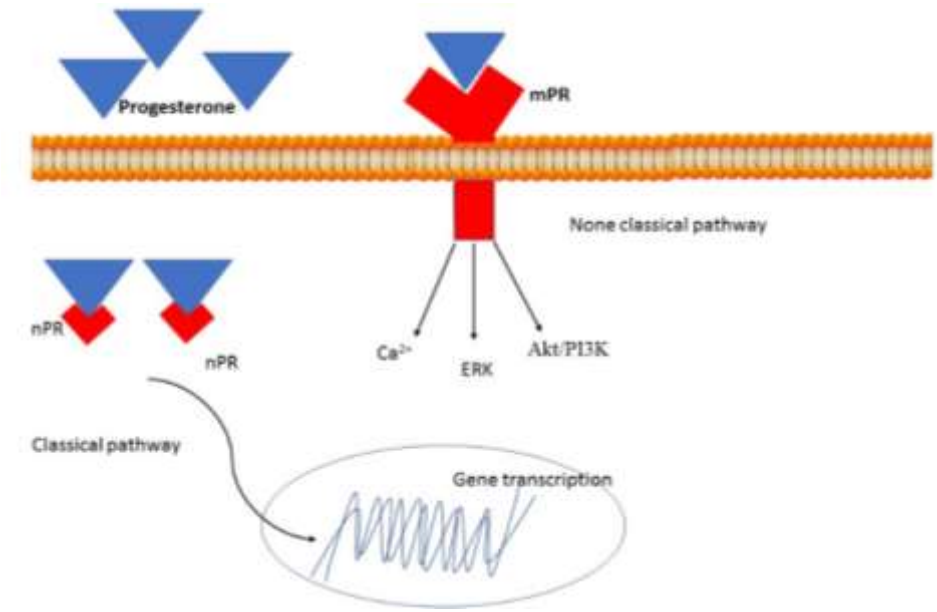

Fig. 2. Effect of progesterone on gut smooth muscle contraction: Progesterone activates its cell surface receptors (mPR), PR that leads to NO production. NO production leads to the generation of cGMP from GTP and in turn activation of PKG. PKG acts to inhibit signaling pathways that provoke contraction such as RhoK and activates the signaling that leads to muscle relaxation such as MLCP. mPR: progeste-rone receptor, NO: Nitric oxide, cGMP: cyclic guánosine monophosphate, GTP: guanosine triphosphate, PKG: protein kinase G, RhoK: Rho kinase, MLCP: myosin light chain phosphatase

Similarly, Colon smooth muscle contractility was increased in the inflammatory bowel syndrome model induced by water immersion and animal restraint in mice and this change was NO-dependent. Progesterone administrations reversed the increased contractility by elevating NO levels [37].

Future directions

Despite the obvious role of progesterone in gastrointestinal tract function, little investigations explored the topic in a mechanistic manner. This necessitates future studies to target the detailed mechanism of action of the inhibitory effect of progesterone on gut motility. Additionally, progesterone function in the GI tract should be studied in a pathological context, such as inflammatory bowel diseases, stress, and during pregnancy and lactation.

Conclusion

Progesterone inhibits gastrointestinal tract motility by acting directly on gut smooth muscle cell surface PRs. This leads to rapid changes in the intracellular second messengers that affect contraction relaxation pathways without the involvement of gene transcription. One of the main downstream second messengers to PRs is NO that acts on Guanylate cyclase to generate cGMP and activation of the subsequent PKG. In turn PKG acts on many molecules in the contraction relaxation pathways to decrease phosphorylation of MLC-20 and eventually inhibition of contraction Fig. 2.

Conflict of Interest

There is no conflict of interest.

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