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Review Article:

Mirabegron-Induced Smooth Muscle Relaxation: Review of the Suggested Mechanisms

Rahma S. Almallah [1], Hani M. Almukhtar [2]

[1] Department of Clinical Pharmacy, College of Pharmacy, University of Mosul, Mosul, Iraq
[2] Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, Iraq

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Abstract

Background: Mirabegron operates through a distinct mechanism compared to antimuscarinic agents. Its activation of β3-adrenoceptors results in the relaxation of the bladder during the filling phase of micturition. The activation of β3-adrenoceptors, which are connected to Gs-proteins, is hypothesized to be the mechanism of mirabegron-induced smooth muscle relaxation. This coupling stimulates adenylyl cyclase, leading to an elevation of intracellular levels of cyclic adenosine monophosphate (cAMP). However, in rat and human corpus cavernosum, mirabegron induces relaxation through distinct mechanisms independently through the nitric oxide/cyclic guanosine monophosphate (NO-cGMP) pathway. Consequently, the precise mechanism by which mirabegron enhances relaxation is still not fully known. **Aim**: The main goal is to delve deeper into the complex mechanisms by which mirabegron causes smooth muscle relaxation in many tissues. **Conclusion**: Mirabegron and similar β3-adrenoceptor agonists hold promise for treating not only overactive bladder but also a range of other conditions including heart failure and metabolic disorders

1. Introduction

1.1 Pharmacology of mirabegron

Mirabegron an extensively specific agonist for β3-adrenergic receptors as opposed to β1 and β2 receptors (1). its effectiveness is marked by substantial relaxation in human and rats bladder smooth muscle. This relaxation occurs through both cAMP-dependent and cAMP-independent pathways, involving the activation of K^+ channels and inhibition of Rho kinase (2). Additionally, mirabegron prompts relaxation in various other tissues, including the prostate, myometrium intestines, gall bladder, pancreas and the pulmonary circulation (2-9).

***Corresponding author:** *Rahma S. Almallah, Department of Clinical Pharmacy, College of Pharmacy, University of Mosul, Mosul, Iraq.*

Email: rahmaalmallah91@gmail.com

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1.2 Smooth muscle contraction and relaxation

Upon contraction, smooth muscle cells experience a reduction in length, facilitating the movement of the organ's contents, or alternatively, changing a tube's diameter to control how its contents flow through it. Irrespective of the triggering stimulus, these cells employ a process known as cross-bridge cycling between actin and myosin to generate force. The contraction process is initiated by calcium ions (Ca^{2+}). Myosin's 20-kDa light chain must be phosphorylated by the enzyme myosin light chain kinase (MLC kinase) in order for contraction to occur. In response to specific signals, the concentration of intracellular Ca^{2+} increases in smooth muscle (10). Ca^{2+} and the protein calmodulin interact with one another, leading to the activation of MLC kinase, which in turn phosphorylates the light chain of myosin. On the other hand, MLC phosphatase (also known as myosin phosphatase), which removes the high-energy phosphate from the myosin light chain, regulates the status of myosin light chain phosphorylation in addition to the Ca^{2+}-dependent activation of MLC kinase (10). This action promotes the smooth muscle relaxation (11). Rho kinase, a serine/threonine kinase, inhibits the action of MLC

phosphatase by phosphorylating the myosin-binding subunit, which promotes the phosphorylated state of the myosin light chain. That is why the small G protein RhoA, along with its downstream target Rho kinase, holds a significant role in the MLC phosphatase activity regulation. By competing with the ATP-binding site on the enzyme, pharmacological inhibitors of Rho kinase interfere with its function leading to relaxation of the smooth muscle (12). Smooth muscles can relax naturally when the stimulus that causes the contraction is withdrawn, or they may relax as a result of substances that directly stop the contractile process. In either case, relaxation requires both an increase in MLC phosphatase activity and a decrease in intracellular Ca^{2+} concentration (11). A number of mechanisms, including those comprising the sarcoplasmic reticulum and the plasma membrane, are thought to be responsible for the decrease in cytosolic Ca^{2+}. By creating and releasing certain chemicals that promote relaxation, the endothelium plays a critical role in regulating the tension of blood vessels (13). These include endothelium-dependent hyperpolarization factors such as nitric oxide (NO), vasodilators prostaglandins such as prostacyclin. The size of the blood artery affects this process. Larger conduit arteries are predominantly regulated by nitric oxide (14), whereas smaller resistance arteries are primarily regulated by endothelium-dependent hyperpolarization factors (15). By illuminating the underlying mechanisms and examining the potential therapeutic consequences, we hope to present an overview of the existing knowledge regarding how mirabegron influences smooth muscle tone in this study.

1.3 Role of NO

Depending on where it is created, how much is produced, and the precise targets in its immediate environment, NO can serve a variety of purposes. As a neurotransmitter, for instance, the small release of NO at nerve endings controls functions such as the relaxation of sphincters in the digestive tract and neurotransmission in the central nervous system. The relaxation state of nearby smooth muscle is controlled by a similar amount of NO released by the vascular endothelium (14). Although NO's actions are primarily localized, it must have the ability to migrate quickly to target areas, frequently in nearby cells, for example: endothelium-derived NO which needs to reach adjacent smooth muscle for relaxation (16). Results have shown that epinephrine modulates the activation of β3-adrenergic receptors in endothelial cells, influencing the activation of endothelial nitric oxide synthase (eNOS). This involves a Rac1-PKA-Akt pathway, which is essential for endothelial cells to migrate (17). The presence of β3-adrenoceptors has been observed in rabbit and human corpus cavernosum (5), leading to the activation of adenylyl cyclase. While the majority of β-adrenergic effects are predominantly mediated through the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) pathway, other cAMP-independent pathways have been discovered. These include the voltage-operated calcium channel closure (18) and the direct activation of potassium (K^+) channels (19). Unlike β1- and β2-adrenoceptors, β3-adrenoceptor activation prompts the release of nitric oxide (NO) and the accumulation of cGMP (20). In the rat thoracic aorta, a study provides evidence that β3-adrenoceptors are primarily located on endothelial cells (21), they collaborate with β1- and β2-adrenoceptors to induce relaxation by activating an NO synthase pathway, leading to increased cyclic GMP levels (22). In fact, β3-adrenoceptor activation significantly contributes to the isoprenaline relaxing effect in the thoracic aorta of rats through the activation of an endothelium-dependent NO synthase pathway (22). Similarly, in human coronary microarteries, the research outlines a novel pathway for adrenergic vasorelaxation via the activation of β3-adrenoceptors located on endothelial cells (23). Functional experiments using β3-adrenoceptors reveal a vasorelaxation with slow kinetics in human coronary microarteries (24). Lastly, in the human cardiac ventricle, where β3-adrenoceptors are linked to the NO pathway, they have been shown to couple with Gi/0 proteins (25, 26).

1.4 Roles of BK_{Ca} channels

Adenylyl cyclase is activated as part of the traditional signaling route of beta-adrenergic receptors which produces cyclic adenosine monophosphate (cAMP). As a result, protein kinase A is activated, which in turn phosphorylates myosin light chain kinase, preventing calcium-calmodulin and myosin/actin from interacting (27). While this could potentially play a role in the relaxation of detrusor smooth muscle, studies utilizing inhibitors of adenylyl cyclase or PKA have found minimal, if any, involvement of this pathway in bladder relaxation. On the contrary, substantial evidence points towards another mechanism wherein β-ARs can activate large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels. Several species, including guinea pigs, rats, mice, and humans, have shown this phenomenon. Iberiotoxin, a BKCa channel inhibitor, greatly decreased the β-AR-induced relaxation induced by Mirabegron and isoprenaline in KCl-contracted detrusor smooth muscle in mouse and rat models (27).

However, even when inhibitors targeting both the cAMP/PKA and the BK_{Ca} pathways were jointly administered, they only managed to inhibit bladder relaxation mediated by β-AR by less than fifty percent, this suggests the potential involvement of other pathways beyond the ones mentioned (28). Urinary bladder relaxation of β-ARs was less pronounced in tissue precontracted with 80 mM KCl in comparison to the relaxation induced with lower KCl contraction. In conclusion, BK_{Ca} channels are involved in the relaxation prompted by β-adrenergic receptors (27, 29).

1.5 Role of cAMP

Mirabegron promotes relaxation, however the precise cellular mechanism underlying this effect is still unknown. The process of smooth muscle relaxation induced by mirabegron involves the coupling of stimulated β3-adrenoceptors to adenylyl cyclase via Gs-proteins. This coupling results in heightened intracellular cAMP levels, subsequently leading to the activation of protein kinase PK A (4, 8).

It is commonly acknowledged that detrusor smooth muscle possesses a more developed Ca^{2+} sensitization mechanism in contrast to other types of smooth muscle. This Ca^{2+} sensitization predominantly operates through two pathways: The protein kinase C (PKC) and Rho kinase pathways. In human detrusor smooth muscle, cAMP primarily suppresses the Rho kinase pathway while only exerting a minor influence on the PKC pathway. This interplay might participate in the manner in which β-adrenoceptor agonists trigger relaxation (4).

Mirabegron's impact extends beyond its interaction with β3-adrenoceptors in bladder smooth muscle. It also engages an intracellular element to induce the inhibition of Ca^{2+} sensitization. In smooth muscle, the primary mechanism

underlying Ca^{2+} sensitization involves an augmentation in myosin light chain phosphorylation. This can occur independently of calcium–calmodulin signaling or through the inhibition of myosin light chain phosphatase (MLCP). It was proposed that mirabegron might directly interact with the system responsible for myosin light chain kinase (MLCK) phosphorylation, resulting in the suppression of the calcium–calmodulin-dependent interaction between myosin and actin. The observed mirabegron effect on detrusor muscle entails the inhibition of Ca^{2+} sensitization, a process situated downstream of the β3-adrenoceptor–cAMP–PKA pathway.

1.6 Role of Rho kinase

Consistent with previous research emphasizing the significant function of Rho-kinase in bladder contraction, the inhibitor of Rho-kinase, Y27,632, exhibited a reduction in contractions caused by both KCl and carbachol in rat models (27). Similarly, it lowered carbachol-triggered contractions in detrusor smooth muscle of human. Despite the established role of Rho-kinase in regulating bladder tone, its influence on β-adrenergic receptor (β-AR)-induced relaxation had not been investigated previously, an evidence suggests that Rho-kinase's involvement in downstream β-AR signaling appears to rely on the specific contractile agonist in use. Mirabegron effectively induced significant relaxation in isolated corpus cavernosum strips by directly engaging b3-adrenoceptors (30), indicating an intimate functional connection between b3-adrenoceptors and the RhoA/ROCK pathway without reliance on the NO-cGMP pathway (31, 32). Additionally, these findings suggest the potential for future clinical investigations involving mirabegron in combination with ROCK inhibitors and phosphodiesterase type 5 inhibitors for managing erectile dysfunction. This approach could be particularly valuable for patients who do not exhibit positive responses to PDE5i therapy.

1.7 Role of Ca^{2+} ion

Mammalian hearts exhibit the presence of β1-, β2-, and β3-adrenergic receptors, which have been demonstrated to modulate cardiac contractility through various mechanisms (33, 34). Stimulation of β1- and β2-adrenergic receptors triggers L-type Ca^{2+} channel activation via a cAMP/protein kinase A signaling pathway, facilitated by Gs proteins. Additionally, β2-adrenergic receptors are coupled with Gi proteins. More lately, the presence of β3-adrenergic receptors has been identified in mammalian hearts, including species like humans, dogs (35), rats, and guinea pigs. Stimulation of β3-adrenergic receptors results in cardiac contractility inhibition through a Gi protein-mediated pathway, as well as a mechanism linked to the nitric-oxide synthase (NOS) system (36, 37). This stimulation-induced reduction in contractility is linked to modifications in action potentials and a decrease in Ca^{2+} transients. The selective β3 agonist BRL-37,344 has been observed to inhibit L-type Ca^{2+} channels and diminish intracellular Ca^{2+} transients in canine ventricular myocytes (38). This effect is accompanied by a dose-dependent decline in contractility (36, 39). By contrast, β3-adrenergic receptors stimulation activates atrial muscle via Ca^{2+} channel activation (37).

1.8 Role of alpha1-Adrenoceptor:

In men, lower urinary tract symptoms encompass obstructive symptoms, which are commonly linked to benign prostatic hyperplasia (BPH). These symptoms can happen independently or concurrently with storage symptoms. The heightened smooth muscle tone in the prostate associated with BPH plays a pivotal role in the pathophysiology and therapeutic approach to obstructive symptoms. As a result, BPH patients may experience difficult urination and reduced bladder emptying as a result of urethral blockage brought on by elevated prostate smooth muscle tone.

As a result, medications aimed at treating lower urinary tract symptoms (LUTS) suggestive of BPH include α1-blockers as the primary choice, along with the phosphodiesterase 5 inhibitor (tadalafil). These drugs are utilized for symptom alleviation by inhibiting prostate smooth muscle contractions. Previous study proposed that mirabegron could potentially function as an antagonist for α1-adrenoceptors, consequently suppressing adrenergic smooth muscle contractions and curtailing neurogenic contractions within the human prostate. These effects were evident at concentrations of 5μM or higher when tested in vitro. On the contrary, mirabegron didn't display any significant impact at 1μM concentration, nor did it affect non-adrenergic contractions or the proliferation of stromal cells. It's evident that mirabegron's effects within the human prostate are primarily due to off-target interactions and necessitate elevated concentrations. However, it's clear that specific β3-adrenoceptor-mediated effects are notably absent (2).

Stimulation of the corpus cavernosum strips using mirabegron at concentrations of 1 μM and 10 μM did not result in an increase in cAMP levels within the tissue. This suggests that mirabegron does not activate adenylyl cyclase to induce cAMP production in this context (32). Other previous research on both the cardiovascular system and rabbit corpus cavernosum has demonstrated that activating β3-adrenoceptors leads to the release of nitric oxide (NO). Notably, the relaxation of corpus cavernosum caused by mirabegron was not affected by the presence of inhibitors such as L-NAME or ODQ (30). Moreover, considering the importance of calcium-dependent potassium (KCa) channels in the relaxation of various smooth muscles, including vascular and nonvascular ones, corpus cavernosum strips that were pre-incubated with a combination of potassium channel inhibitors did not exhibit any change in the relaxation induced by mirabegron, in addition mirabegron did not interfere with $CaCl_2$-induced contractions, suggesting it doesn't function as a blocker of calcium influx. Alternatively, another study by De Oliveira et al demonstrated that mirabegron induced relaxation in rat corpus cavernosum both in vitro and improved erectile function in vivo (20). These effects were attributed to mechanisms unrelated to β3-adrenoceptor activation but linked to the antagonism of α1-adrenoceptors (40). It's important to note that these findings don't necessarily imply that mirabegron doesn't act as a β3-adrenoceptor agonist in tissues from different species. Nonetheless, caution is advised when extrapolating the effects of mirabegron to clinical settings, particularly when utilizing rats as a model for studying erectile dysfunction (30, 31).

1.9 Role of muscarinic receptor

Mirabegron's capacity to reduce the release of acetylcholine from cholinergic nerves in the urinary bladder has been demonstrated in both rat and human studies (41). Mirabegron also appears to operate as an antagonist to muscarinic receptors in the bladder (42). The particular mechanisms underlying these impacts are still unknown, though. According to information provided to the Food and

Drug Administration by Astellas Co., Ltd., mirabegron had a Ki value of 2.1 mM and demonstrated binding affinity to human M2 muscarinic receptors (41, 43). The combined therapy of solifenacin and mirabegron has been linked to a higher incidence of anticholinergic adverse effects, such as dry mouth, compared to solifenacin alone (42). In fact, another research reported an elevated occurrence of constipation, dry mouth, and dyspepsia with the combination therapy, as opposed to monotherapies (44). This suggests that the increased prevalence of anticholinergic side effects with mirabegron-solifenacin concomitant therapy might be attributed to mirabegron's antagonistic impact on muscarinic receptors, along with its β3 agonistic properties. The findings obtained from rat bladder studies in this context lend support to the clinical relevance of mirabegron's ability to block muscarinic receptors.

It is plausible to propose that the perceived effectiveness of mirabegron in relaxing detrusor muscle solely through β3-adrenoceptor agonism could potentially be exaggerated, possibly arising from its ability to also act as an antagonist to M3 receptors. However, this assertion warrants additional in-depth investigation for clarification (45, 46).

2. Conclusion

In summary, mirabegron and similar β3-adrenoceptor agonists hold promise for treating not only overactive bladder but also a range of other conditions including heart failure and metabolic disorders. Future research efforts should focus on investigating the off-target effects, as well as any indirect signaling pathways, associated with mirabegron in particular those associated with smooth muscle relaxation. It is also important to determine whether these off-target actions have any significant clinical implications.

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استرخاء العضلات الملساء الناجم عن دواء الميرابغرون :مراجعة الاليات المقترحة

الخلاصة

المقدمة: يعمل ميرابيغرون من خلال آلية متميزة مقارنة بالعوامل المضادة للمسكارين. يؤدي تنشيطه للمستقبلات الأدرينالية β3 إلى استرخاء المثانة أثناء مرحلة امتلاء التبول. يُفترض أن تنشيط المستقبلات الأدرينالية3β ، المرتبطة ببروتينات Gs ، هو آلية استرخاء العضلات الملساء الناجم عن الميرابيغرون. يحفز هذا الاقتران إنزيم محلقة الأدينيل، مما يؤدي إلى ارتفاع مستويات أحادي فوسفات الأدينوزين الحلقي (cAMP) داخل الخلايا. ومع ذلك، في الجسم الكهفي للجرذان والبشر، يحفز ميرابيغرون الاسترخاء من خلال آليات متميزة بشكل مستقل من خلال مسار أكسيد النيتريك/أحادي فوسفات الجوانوزين الحلقي. (NO-cGMP) وبالتالي، فإن الآلية الدقيقة التي يعزز بها الميرابيغرون الاسترخاء لا تزال غير معروفة تمامًا. **الهدف**: الهدف الرئيسي هو التعمق في الآليات المعقدة التي من خلالها يتسبب الميرابيغرون في استرخاء العضلات الملساء في العديد من الأنسجة. **الاستنتاج**: إن عقار ميرابيغرون ومحفزات مستقبلات بيتا 3 الأدرينالية يبشر بالخير ليس فقط في علاج فرط نشاط المثانة ولكن أيضًا في علاج مجموعة من الحالات الأخرى بما في ذلك قصور القلب والاضطرابات الأيضية.

الكلمات المفتاحية: ميرابغرون، استرخاء، قنوات البوتاسيوم الموجبة، اوكسيد النتريك، أحادي فوسفات الأدينوزين الحلقي،العضلات الملساء