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Current possibilities and prospects of tocolytic therapy

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ABSTRACT

The urgency of the problem of preterm birth (PB) is because of its high prevalence and neonatal mortality. The effects of PB on the fetus are often fatal, and PB accounts for 70% of neonatal mortality and 36% of infant mortality. Severe neurological deficits (e.g., cerebral palsy, epilepsy, intraventricular hemorrhages, retinopathy, blindness, hearing loss, delayed neuropsychiatric and motor development) occur in 68% of surviving premature infants. Additionally, children born prematurely have a high risk for purulent septic diseases. The metabolic consequences of prematurity cause diseases such as metabolic syndrome and hypertension. Thus, tocolytic therapy is a crucial therapeutic measure in obstetrics. However, most known and actively used tocolytic drugs induce insufficient effect for long-term prolongation of pregnancy or have serious side effects. Currently, there is a search for new tocolytics to obtain safe, adequate, and long-term effects. This review examines promising and relevant drugs that may be used in routine obstetric practice. Scientific articles, meta-analyses, and systematic reviews from the databases PubMed, Embase, Web of Science, and Google Scholar, and RSCI were analyzed. For the analysis, publications in English and posted no more than 5 years before the study was conducted were selected, except for fundamental works with a longer publication period.

Keywords: preterm birth; tocolysis; tocolytic therapy.

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Токолиз в современном акушерстве: возможные перспективы

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АННОТАЦИЯ

Актуальность проблемы преждевременных родов (ПР) обусловлена высокой распространённостью и неонатальной смертностью. Последствия ПР для плода часто бывают фатальными: на их долю приходится 70% неонатальной смертности и 36% — младенческой. Тяжёлый неврологический дефицит (детский церебральный паралич, эпилепсия, внутрижелудочковые кровоизлияния, ретинопатия, слепота, потеря слуха, задержка нервно-психического и моторного развития) присутствует у 68% выживших недоношенных детей. Кроме того, дети, преждевременно рождённые, имеют высокий риск гнойно-септических заболеваний. Метаболические последствия недоношенности формируют предпосылки для развития таких заболеваний, как метаболический синдром и артериальная гипертензия. В этой связи весьма важным и актуальным лечебным мероприятием в акушерстве является токолитическая терапия. Однако большинство известных и активно применяющихся токолитических препаратов обладают недостаточным для длительного пролонгирования беременности результатом или ассоциированы с серьёзными побочными эффектами. В настоящее время идёт активный поиск новых токолитиков с целью получения наиболее безопасного, мощного и долгосрочного эффекта. В данной обзорной статье рассмотрены наиболее перспективные и актуальные препараты, которые имеют хорошие шансы войти в рутинную акушерскую практику. Для этого проанализированы научные работы, метаанализы, систематические обзоры, находящиеся в открытом доступе в базах данных PubMed, Embase, Web of Science, Google Scholar и РИНЦ. Для анализа преимущественно отбирали публикации, вышедшие на английском языке и размещённые в базах данных не более пяти лет назад, за исключением фундаментальных работ с более давним сроком публикации.

Ключевые слова: преждевременные роды; токолиз; токолитическая терапия.

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现代产科中的分娩镇痛：可能的前景

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摘要

早产问题之所以紧迫，是因为其发病率和新生儿死亡率都很高。早产对胎儿的影响往往是致命的：占新生儿死亡率的70%，占婴儿死亡率的36%。68%的存活早产儿存在严重的神经系统缺陷（脑瘫、癫痫、脑室出血、视网膜病变、失明、听力损失、神经精神和运动发育迟缓）。此外，早产儿患化脓性败血症的风险也很高。早产的代谢影响是代谢综合征和高血压等疾病发展的先决条件。在这方面，溶血疗法是产科中非常重要和相关的治疗措施。然而，大多数已知和积极使用的促溶血药物在延长妊娠期方面效果不佳，或伴有严重的副作用。为了获得最安全、最有效和最持久的疗效，人们正在积极寻找新的促溶血药物。这篇综述文章探讨了最有希望进入常规产科实践的相关药物。为此，我们分析了开放数据库PubMed, Embase, Web of Science, Google Scholar和RSCI中的科学论文、荟萃分析和系统综述。为了进行分析，主要选择了不超过五年前在数据库中发布的英文出版物，但出版时间较长的基础著作除外。

关键词： 早产；溶胎；溶胎疗法。

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INTRODUCTION

Preterm birth (PB), or births between 22 and 36 weeks of gestation, remains a pressing global public health problem, accounting for approximately 11.5% of all births in developed countries and being associated with approximately 80% of infant mortality and morbidity. PB is a pressing medical issue because, despite a large number of studies, the exact etiology and pathogenesis of this condition have not been determined. The incidence of PB has been significantly reduced and does not exceed 10%–15% in developed countries [1, 2].

The following factors have contributed to improved perinatal outcomes. The widespread use of agents such as progesterone, oxytocin receptor antagonists to prolong pregnancy, magnesium sulfate to neuroprotect the fetal brain, and surfactant administration improve perinatal outcomes in preterm infants and reduce neonatal morbidity and mortality. Pharmacotherapy is the most effective and efficient method of prevention and treatment of PB. Our paper reviews modern literature data on the most effective and safe tocolytics.

TRADITIONAL TOCOLYTIC THERAPY

Tocolytic therapy is one of the most important measures to reduce the incidence of PB.

Tocolysis is indicated for PB, which is clinically defined as having at least four contractions in 20 minutes and dynamic cervical changes. Tocolysis is performed at 24 to 34 weeks of gestation [2]. Traditional tocolytics include calcium channel blockers, oxytocin receptor antagonists, cyclooxygenase inhibitors, beta2-adrenergic agonists, magnesium sulfate, progesterone, and nitric oxide (NO) donors.

Calcium channel blockers (calcium antagonists)

Nifedipine is the best studied and most commonly used calcium channel blocker. This agent blocks L-type calcium channels located in myometrial cells. Blocking slow L-type calcium channels inhibits calcium ion transport across the myometrial smooth muscle cell membrane. This reduces intramyocyte calcium accumulation without affecting plasma calcium concentrations. Without calcium ions, there is no actin-myosin interaction necessary for smooth muscle cell contraction. As a result, myometrial contraction, which provides the tocolytic effect of nifedipine, does not occur. When nifedipine was compared with beta2-adrenergic agonists, a more significant tocolytic effect of nifedipine was observed with fewer side effects, including skin hyperemia, allergic reactions, tachycardia, hypotension, peripheral edema, dyspeptic disorders, elevated transaminases, intrahepatic cholestasis, and headache [2]. Prolonged use at high doses may cause side effects such as paresthesia and myalgia, tremor, visual disturbances, insomnia, and increased daily urine output. Prolonged use at high doses may also cause kidney dysfunction [3].

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Some NSAIDs (indomethacin) are used to treat life-threatening PB by inhibiting cyclooxygenase-2 and decreasing the synthesis of prostaglandins E2 and F2a [4]. This treatment is based on pathogenetic mechanisms, since prostaglandins are known to play an important role in development of labor. Prolonged use of these agents is associated with side effects such as stomach ulcers (ulcerogenic effect), decreased platelet aggregation, stomach hemorrhage, aspirin-induced asthma, bronchospasm, and kidney dysfunction. This agent should not be used for more than three days to avoid premature closure of the fetal ductus arteriosus and oligohydramnios.

Beta2-adrenergic agonists

Hexoprenaline, salbutamol, and fenoterol are currently the most commonly used agents in this group. Hexoprenaline is particularly widespread in the Russian Federation. This agent is proved to be effective in prolonging pregnancy for up to two days. Hexoprenaline reduces myometrial contractile activity by stimulating postsynaptic beta2-adrenergic receptors coupled to Gs proteins. These proteins stimulate adenylate cyclase, leading to an increase in cyclic adenosine monophosphate (cAMP) levels, activation of cAMP-dependent protein kinase in smooth muscle cells, which inhibits myosin light-chain kinase, preventing phosphorylation of myosin light chains and interaction with actin. In addition, cAMP-dependent protein kinase inhibits phospholamban, resulting in elevated calcium-activated adenosine triphosphatase (ATPase) activity and a decrease in cytoplasmic calcium concentration. All of these factors lead to a decrease in myometrial tone and contractility [5]. However, β2-adrenergic agonists have many contraindications such as maternal cardiovascular disease (tachyarrhythmias and other cardiac arrhythmias, congenital and acquired heart defects), hyperthyroidism, closed-angle glaucoma, insulin-dependent diabetes mellitus, and fetal distress not associated with uterine hypertonicity. In addition, these agents have many maternal (nausea, vomiting, headache, hypokalemia, elevated blood glucose, CNS disturbances, tremor, tachycardia, respiratory distress, pulmonary edema) and fetal (tachycardia, hyperbilirubinemia, hypocalcemia) side effects.

Magnesium sulfate

There are no current recommendations for the use of magnesium sulfate as a tocolytic. Magnesium sulfate is not approved as a tocolytic in most countries, but it is used in pregnant women to treat hypomagnesemia, pre-eclampsia, and eclampsia. The tocolytic effect results from magnesium ion-induced inhibition of myometrial contractility (reduced absorption, binding and distribution of calcium ions in smooth myocytes), increased uterine blood flow as a result of the vasodilatory effect due to blocking of slow calcium channels of the smooth myometrial myocytes. Intravenous use may cause some side effects associated with hypermagnesemia,

such as bradycardia, diplopia, hyperemia, diaphoresis, hypotension, cardiac and CNS depression, headache, anxiety, weakness, uterine atony, secondary hypocalcemia with evidence of secondary tetany. Some studies show a reduced risk of cerebral palsy in children born before 32 weeks of gestation [6]. Therefore, magnesium sulfate is currently used for fetal neuroprotection in PB.

Nitric oxide donors

Another group of tocolytics includes NO donors. However, these agents are almost never used routinely. Nitrates interact with SH groups of smooth muscle cells in the vascular wall, leading to release of NO, a potent endothelium relaxing factor, which causes activation of guanylate cyclase, resulting in an increase in cyclic guanosine monophosphate (cGMP). Increased cGMP in smooth muscle cells activates myosin light chain kinases, resulting in relaxing smooth muscle [7]. Therefore, nitroglycerin may also be used as a tocolytic. However, there is no convincing evidence to support or refute its efficacy. Side effects may include headache, orthostatic hypotension, a sharp drop in blood pressure, allergic reactions, and pyrexia.

Progesterone products

In Russia, micronized progesterone with a chemical structure identical to endogenous progesterone is used for the management of PB, which determines the main pharmacological and metabolic effects of this agent [8]. Micronization provides optimal absorption and bioavailability. The effect of micronized progesterone on the uterus in case of threatened PB is caused not only by the direct action of progesterone, but also by the specific properties of its metabolites formed after oral use due to the presence of the group of β-metabolites such as 5β-pregnanedione and 5β-pregnanolone, which have a tocolytic effect. This effect is achieved by inhibiting the binding of endogenous oxytocin to uterine receptors (5β-pregnanedione) as well as to serotonin, acetylcholine, and prostaglandin E2 receptors (5β-pregnanolone) [9].

Oxytocin receptor antagonists

Studies show that atosiban is more effective than hexoprenaline and nifedipine in prolonging pregnancy for more than 7 days. In addition, one in three patients was able to carry pregnancy to term after treatment with atosiban (33.3% and 22.6%, respectively) [3, 10]. Atosiban was the first synthetic oxytocin receptor antagonist. The nonapeptide 1-deamino-2-D-tyr(O-ethyl)-4-trionin-8-orn-oxytocin, called atosiban, blocks not only oxytocin receptors but also V1A receptors, one of the three types of vasopressin receptors, which also include V1B and V2 receptors [10]. Oxytocin is known to have a uterotonic effect by activating both oxytocin receptors and V1A receptors, so the ability of atosiban to block V1A receptors is likely to complement its tocolytic potential effect.

Several studies, including multicenter trials, evaluated the tocolytic effect of intravenous atosiban and its effect on the maternal-fetal system compared to other widely used tocolytics. These studies show that atosiban, like the above-mentioned tocolytics, can delay labor by 2–7 days, allowing the fetus to be prepared for delivery. The lower incidence of side effects in both mother and fetus is an important advantage.

However, there is insufficient evidence to demonstrate that atosiban is superior to other tocolytics in terms of effect and neonatal outcomes. For example, according to literature data [6, 10], there are no differences between atosiban and nifedipine in terms of perinatal outcomes and inhibition of uterine contractility. Therefore, tocolysis with atosiban may be the treatment of choice for PB, especially in women with cardiovascular disease and multiple pregnancies. In recent years, it has been generally recommended to start tocolysis with atosiban or nifedipine for 48 hours because it provides a good result with the fewest side effects. However, the positive effect of this therapy is not achieved in 100% of cases.

Some authors suggest using atosiban in combination with other tocolytics, including nifedipine, beta2-adrenergic agonists such as ritodrine, nitrogen donors, or magnesium sulfate. The benefit of such combined tocolytic therapy was demonstrated for oxytocin-induced myometrial contractions in isolated pregnant myometrium [11]. Tocolytic therapy with atosiban has limitations related to increased amniotic membrane synthesis of prostaglandins E2 and F2A and the proinflammatory cytokines IL-6 and CCL5, as demonstrated in primary human amniocyte experiments [10]. Studies show that atosiban-induced activation of prostaglandin and cytokine synthesis involves Gαi protein, which activates the transcription factor NF-κBp65, leading to activation of MAP kinases. ERK1/2 and p38 protein kinases are predominantly activated. Another reason for the ineffective use of atosiban as a tocolytic may be atosiban ability to reduce efficacy of activating beta2-adrenergic receptors of the myometrium, leading to inhibition of effects of the beta-adrenergic receptor inhibitory mechanism (beta-ARIM) on uterine tone [3, 10]. In fact, experiments show that atosiban reduces the ability of adrenaline to inhibit spontaneous contractile activity of longitudinal strips of the uterine horn of non-pregnant rats. Study data suggest that atosiban is best used with tocolytics such as NSAIDs and beta2-adrenergic agonists. The low bioavailability of atosiban and the need for parenteral use and hospitalization also limit its potential for widespread use. Therefore, new oxytocin receptor antagonists, including those suitable for oral use, should be discovered. In recent years, the potential clinical use of a new peptide oxytocin receptor blocker, barusiban, has been discussed. This oxytocin receptor antagonist is more selective than atosiban. Barusiban is an oxytocin-based peptide antagonist of oxytocin receptors. Its selectivity for oxytocin receptors is actually higher than for V1A or V2 receptors. Barusiban has

a greater efficacy and duration of blockade than atosiban. *In vivo*, barusiban blocks oxytocin-induced uterine contractility in pregnant monkeys. However, in women at risk of late pregnancy loss, barusiban was not effective, as shown in a 21-center trial conducted across several European countries [11]. At the same time, the selective V1A receptor blocker relcovaptan or SR49059 proved to be more effective than barusiban in this case. This suggests that PB may be caused by either premature expression of oxytocin receptors in the myometrium or expression of vasopressin receptors. At that, a V1A receptor antagonist, SR49059, may be effective in treatment of dysmenorrhea.

The synthesis of non-peptide oxytocin receptor antagonists is under active investigation as they are expected to be more bioavailable than the peptide forms of atosiban or barusiban. For example, L368899, GSK221149A (retosiban), WAY1627720, and SSR-126768A have been synthesized and are now in preclinical phase [12]. L368899 is a potent oxytocin receptor antagonist. Its advantage consists in its ability to cross the blood-brain barrier, which may be of additional value in treatment of mental disorders associated with dysfunction of oxytocinergic neurons (autism or schizophrenia). GSK221149A (retosiban) has the highest affinity for vasopressin receptors (V1A and V2) and is 15 times more effective than atosiban at blocking oxytocin receptors [13]. In non-pregnant rats, both oral and parenteral use of retosiban produced a sustained reduction in oxytocin-induced myometrial contractions. It should be noted that in pregnant rats, intravenous use of retosiban completely blocks uterine contractility. SSR-126768A is characterized by rapid onset and long duration of tocolytic action. In experiments with isolated myometrium from non-pregnant rats, this agent blocked oxytocin-induced contractions. Oral use also blocked oxytocin-induced myometrial contractions in experimental rats at a systemic level. Like other non-peptide blockers, WAY1627720 is expected to have good tocolytic potential [14].

FUTURE OF TOCOLYTICS

Antagonists of prostaglandin receptors

OBE002 is a potent and selective prostaglandin PGF2α receptor antagonist for oral use as a small molecule prodrug. Inhibiting PGF2α receptors reduces inflammatory activity, decreases uterine tone, and protects against rupture of membranes, which are associated with PB. This oral valine ester prodrug is readily hydrolyzed to an equally potent and highly selective PGF2α antagonist metabolite called OBE002. Several studies confirmed that the prodrug significantly reduced spontaneous uterine contractions in pregnant rats without affecting the ductus arteriosus, kidneys, or coagulation processes [15, 16]. These studies were used to assess the use of this drug candidate in patients with PB. Clinical trials are ongoing to evaluate its safety, efficacy, and pharmacokinetic profile in pregnant women with PB.

Unlike indomethacin, OBE002 does not have fetal side effects associated with inhibition of prostaglandin synthesis [17, 18]. The combination of OBE002 with other treatments may have additive or synergistic effects on uterine contractions, thereby prolonging pregnancy.

Non-selective phosphodiesterase inhibitors

The tocolytic effect of aminophylline (theophylline) is thought to be caused by selective inhibition of specific phosphodiesterases, leading to an increase in intracellular cAMP concentration, a decrease in intracellular calcium concentration, and ultimately myometrial relaxation [19–23]. *In vitro* experiments show that type III and type IV isozymes seem to play the key role. Some of the side effects of aminophylline (theophylline), including vomiting, hypotension, and tachycardia, may also be caused by inhibition of these isozymes.

However, use of aminophylline in PB may result in potentially dangerous plasma concentrations of theophylline and caffeine in newborns. Newborns whose mothers received aminophylline during pregnancy (especially during the third trimester) require monitoring for theophylline toxicity. Theophylline is excreted in human milk. If aminophylline is used by a breastfeeding mother, an infant may become irritable.

Therefore, aminophylline may be used during pregnancy and lactation (breast-feeding) if the expected maternal benefit outweighs the potential fetal or neonatal risk.

2-APB, glycyl-H-1152, and HC-067047 are inhibitors of intracellular signaling pathways that induce myometrial contractility.

Tocolytics target intracellular pathways that regulate myometrial contractility. 2-APB, glycyl-H-1152, and HC-067047 are identified as inhibitors of uterine contractility with tocolytic potential. However, efficacy of the new agents is not fully understood and is not compared with more thoroughly studied established drugs, such as phosphodiesterase inhibitors aminophylline and rolipram, or clinically used nifedipine and indomethacin.

HC-067047 is an inhibitor of the *transient receptor potential subfamily V, member 4* (*TRPV4*), a non-selective cation channel that is permeable to extracellular Ca^{2+} [24–27]. *TRPV4* is activated by physiological labor triggers. By inhibiting *TRPV4* channels, HC-067047 prevents the influx of extracellular Ca^{2+} through these channels, thereby preventing an increase in intracellular Ca^{2+} and myometrial contractility. *TRPV4* is highly expressed in the myometrium of pregnant women. *TRPV4* levels increase during pregnancy. These data suggest that *TRPV4* inhibition may be a potential novel tocolytic strategy. However, effects of *TRPV4* inhibitors like HC-067047 on spontaneous myometrial contractions in pregnancy are not evaluated.

2-APB was originally developed to inhibit inositol trisphosphate receptors (IP3, IP3R) [28]. Therefore, 2-APB nonspecifically inhibits both IP3R and calcium channels, as

well as other Ca^{2+} transporters such as sarcoplasmic Ca^{2+}-ATPase pumps, and TRPC family channels [29–33]. Since its discovery, several studies have tested 2-APB in rodent myometrial strips and have found that 2-APB inhibits both agonist-stimulated myometrial contractions (by oxytocin, pennogenin tetraglycoside, *Lannea acida* extract, *Ficus deltoidea* extract) and spontaneous myometrial contractions [34]. Although 2-APB effectively inhibits uterine contractility in pregnant rodents, effects of 2-APB on spontaneous myometrial contractions in humans have not been evaluated.

Further studies are needed to evaluate tocolytic efficacy and safety of these agents *in vivo* using PB models.

Small-molecule inhibitors of TLR4 signaling

There is compelling evidence that exposure to pro-inflammatory mediators is an important factor in the fetal inflammatory response syndrome often associated with PB. Toll-like receptors (TLRs) are critical inflammatory triggers. TLR4s play a central role due to their ability to sense and integrate signals from various microbial and endogenous triggers to induce and maintain inflammation. Preclinical studies have identified TLR4 as an attractive pharmacological target for promoting uterine quiescence and protecting a fetus from inflammatory injury.

Novel small-molecule inhibitors of TLR4 signaling, particularly the opioid receptor antagonists naloxone and naltrexone, are found to effective in preventing heat-killed bacterial lipopolysaccharide mimetic-induced PB in animal models.

This group of compounds has several advantages, including relative ease of synthesis, stability during handling and transport, and potential suitability for use in resource-limited settings where most infant mortality occurs. In addition, they readily cross the placenta. Based on data on (-)-naloxone (the negative isomer), they are considered safe for pregnant women and newborns [35, 36].

Further studies are required to evaluate safety and efficacy of naloxone products [37]. For example, the risk of non-specific immune suppression and its effect on maternal protection against infections should be evaluated.

However, all of these agents have limitations, the most important of which are maternal and fetal side effects, a weak effect of tocolysis that may only delay labor for a short time, and novelty that requires further randomized multicenter prospective studies.

Development of multidrug combinations is a promising direction in tocolytic therapy. Adding a tocolytic agent to therapy may help reduce the treatment dose to prevent side effects.

Calcium-activated chloride channel antagonists, Anoctamin-1 (ANO1)

This is a new class of drug candidates to be used in combination therapy with nifedipine. Because ANO1 blockade hyperpolarizes myometrial cell membranes, impairing excitation and contraction, combined effects of ANO1 inhibitors and nifedipine limit Ca^{2+} current and produce opposite synergism at lower doses of each tocolytic.

In addition, ANO1 antagonists are new candidates for combination therapy with beta2-adrenergic agonists. β2AR is a G protein-coupled receptor that activates adenylate cyclase, increases cAMP levels, and activates protein kinase A [38, 39]. As a result, protein kinase A inhibits myosin light chain phosphorylation, which promotes smooth muscle relaxation. There is evidence that β2AR agonism activates Ca^{2+}/calmodulin-dependent protein kinase II, which specifically inhibits ANO1. β2AR activation may influence ANO1 activity in labor via CaMKII-mediated inhibition. Therefore, beta2-adrenergic agonists and ANO1 antagonists may have a synergistic effect on myometrial relaxation using low doses of each agent as a new potential therapy.

Combination therapy of an OBE002 prostaglandin receptor antagonist with other tocolytics

In contrast to indomethacin, OBE002 is not associated with fetal harm related to inhibition of prostaglandin synthesis [40]. The combination of OBE002 with other treatments may have additive or synergistic effects on uterine contractions, thereby prolonging pregnancy.

The use of OBE022, a PGF2α antagonist prodrug, in combination with standard therapies and other tocolytics may provide new alternatives for treatment of PB. Nifedipine doses could potentially be reduced and/or used incrementally when co-administered with OBE022. No clinically significant pharmacokinetic interactions were observed between the OBE022 prodrug and magnesium sulfate, betamethasone, or atosiban. However, effects of nifedipine were significantly enhanced. Co-administration of OBE022 with magnesium sulfate, betamethasone, atosiban, and nifedipine does not raise concerns and may provide new effective alternatives for treatment of PB [41].

CONCLUSION

At present, it is challenging to ascertain which tocolytic agent is the optimal treatment option. Tocolytics, which are well known and actively used in clinical practice, are not likely to reliably and safely prolong pregnancy in all cases. Therefore, search for more active, effective, and selective tocolytics needed to stop PB, reduce myometrial contractile activity during in vitro fertilization (IVF), and acute tocolysis during labor (for fetal health) remains the most relevant direction for obstetric practice. The evaluation and search for antagonists of PB signaling pathways is a promising and challenging area of research aimed at the complete control of PB.

ADDITIONAL INFO

Authors' contribution. A.O. Kiryanova — conception and design of the study, collection and processing of material, writing and editing of the text; A.V. Murashko — conception and design of the

study, collection and processing of material, editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work).

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