South Afr J Anaesth Analg. 2023;29(5 Suppl 1):S125-128
https://doi.org/10.36303/SAJAA.3031

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173

FCA REFRESHER COURSE

Drug action on the myometrium

T Kleyenstuber

Department of Anaesthesia, School of Clinical Medicine, Faculty of Health Sciences, Rahima Moosa Mother and Child Hospital, University of the Witwatersrand, South Africa
Corresponding author, email: *t.kleyenstuber@gmail.com*

Keywords: uterine contraction, uterine relaxation, uterotonics, tocolytics

Introduction

The mechanisms responsible for uterine contraction have been extensively explored. A reasonable insight into these mechanisms is required to understand the pharmacology of drugs that induce and maintain uterine contraction (uterotonics) and relax the uterus (tocolytics). Both the uterotonic and tocolytic drugs are used extensively in current obstetric practice and the associated side effects are not uncommon. Some of our anaesthetic drugs also act on the myometrium.

Overview of uterine contraction and relaxation

Spontaneous changes in the electrical activity of myometrial cells (mechanism unknown) induce membrane depolarisation, which opens voltage-gated L-type calcium channels and allows the influx of calcium into the cytosol. The calcium binds to calmodulin and activates myosin light-chain kinase (MLCK). The resultant ATP-dependent phosphorylation of myosin light chains allows the interaction of myosin and actin, cross-bridge formation, and force development.[1–3] This entire process is depicted in Figure 1.

Myosin light-chain phosphatase (MLCP) dephosphorylates myosin, thereby reducing myosin ATPase activity and muscle tension. The opposing effects (phosphorylation versus dephosphorylation of myosin) of MLCK and MLCP are dependent on the intracellular calcium concentration. The myometrial smooth muscle relaxes when the intracellular calcium concentration decreases due to calcium extrusion from the cell or sarcoplasmic uptake. This reduces MLCK activity and allows the dephosphorylation of myosin by MLCP.[1,2]

The regulation of these pathways is complex and not completely understood. Several second-messenger systems are involved and provide further potential targets for drugs. Various prostaglandins (PGs) also exert their effect on the myometrium. Each of these PGs binds to its specific G-protein-coupled receptor.[1,2] The mechanisms of the different PGs will be explored later. Furthermore, gap junctions between individual myometrial smooth muscle cells allow coordinated uterine contraction.[2]

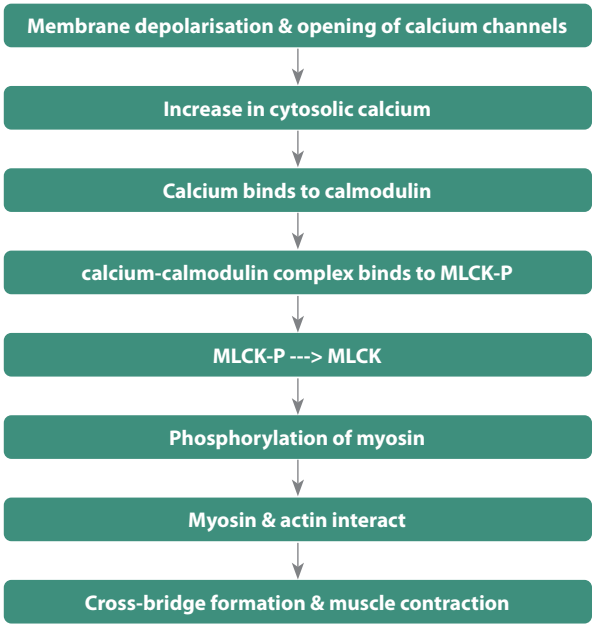

Figure 1: Uterine smooth muscle contraction process
MLCK – myosin light-chain kinase, MLCK-P – phosphorylated (inactive) MLCK

Relevant physiological changes during pregnancy and labour

The expression of myometrial oxytocin receptors (OXTRs) is upregulated significantly and progressively during pregnancy and the number and concentration of these receptors peak during early labour. In contrast, the release of oxytocin does not change during pregnancy and early labour. However, an increase in oxytocin release does occur during the crowning of the fetal head and lasts until the delivery of the placenta.[1]

PG production gradually increases during the first stage of labour, followed by a more rapid increase during the second stage, and a peak at the time of delivery of the placenta.[1] Pregnancy is also associated with an increase in myometrial gap junctions.[3,4]

Uterotonics

Indications for the use of uterotonics are:

1. induction of labour or termination of pregnancy;
2. augmentation of slowly progressing labour;

3. promoting the delivery of the placenta; and

4. reducing postpartum bleeding.[2]

Oxytocin

Oxytocin is a nonapeptide hormone naturally released in pulses from the posterior pituitary gland and is structurally similar to vasopressin. The synthetic form of oxytocin is the drug syntocinon.[2]

Oxytocin is usually administered intravenously as it is inactivated in the stomach. It does not bind to plasma proteins and is metabolised by the kidneys and liver, with a circulating half-life of 10–15 minutes.[5]

The OXTR is a G-protein-coupled receptor with seven transmembrane domains. Binding of oxytocin to its receptor results in the production of inositol triphosphate (IP3) and diacylglycerol (DAG) via the effect of phospholipase C (PLC) on phosphatidylinositol bisphosphate (PIP2). IP3 triggers the release of calcium from the sarcoplasmic reticulum (SR). The calcium then binds to calmodulin and initiates the myometrial contraction pathway as described earlier. DAG stimulates PG synthesis. Oxytocin also activates and increases cyclooxygenase (COX) 2, resulting in further PG production.[1–3]

Other mechanisms of action of oxytocin include the inhibition of MLCP, inhibition of calcium efflux from the cytoplasm, and stimulation of nitric oxide (NO) production. OXTRs are also present in vascular and renal endothelium, as well as cardiac myocytes. It has been proposed that the release of NO mediates the vasodilatation and natriuresis commonly seen after oxytocin administration.[1]

Other than myometrial contraction, oxytocin has several other physiological effects and influences the cardiovascular system, maternal and sexual behaviour, and memory formation.[3]

Oxytocin has a narrow therapeutic range and is associated with significant cardiovascular side effects. Peripheral vasodilatation, hypotension, and increased cardiac output are common. The cardiac output is increased by an increase of both heart rate and stroke volume and has a protective effect in most patients. Hypotension is likely due to NO-induced vascular smooth muscle relaxation. At relatively large bolus doses (10 IU), myocardial ischaemia may occur and pulmonary artery pressures may be increased. These changes may cause considerable cardiovascular instability in patients who cannot increase their cardiac output, such as those who are hypovolaemic, have reduced ventricular function, or have stenotic lesions of their mitral or aortic valves.[3,6]

A moderate antidiuretic effect is attributed to oxytocin's structural similarity to vasopressin. In excessive doses, oxytocin may cause water retention and hyponatraemia. Non-cardiovascular side effects of oxytocin include nausea, vomiting, flushing, and headaches.[3,4]

The administration of oxytocin during augmentation of labour may increase the risk of uterine hyperstimulation and fetal distress. Placental perfusion may be reduced when uterine blood vessels are occluded by an excessively contracted myometrium.[2]

OXTR desensitisation is a concern when oxytocin is infused during induction or augmentation of labour. The ED90 in oxytocin-naïve patients during caesarean delivery is 0.35 IU, but after oxytocin augmentation, the ED90 is 3.0 IU. Repeated doses or prolonged infusions of oxytocin seem to decrease its clinical effectiveness, and second-line uterotonics should be considered in these patients. There is also some evidence suggesting that the haemodynamic response to a second dose of oxytocin is less.[3,6]

Carbetocin

Carbetocin (1-desamino-1-monocarbo-[2-O-methyltyrosine]-oxytocin) is a long-acting synthetic oxytocin analogue with a half-life of 50 minutes. It binds exclusively to OXTR in the myometrium and stimulates rhythmic contractions, increases the frequency of contractions, and increases uterine tone. Uterine contraction is produced two minutes after administration, irrespective of route. The rhythmic contractions persist for 60 minutes after intravenous injection (IVI) and 120 minutes after intramuscular injection (IMI).[1,3]

Carbetocin is currently only registered for the management of post-partum uterine atony. The side effect profile is similar to oxytocin and similar haemodynamic effects should be expected. Contraindications include hepatic, renal, and severe cardiovascular disease, epilepsy, as well as preeclampsia and eclampsia.[1,3]

Ergot alkaloids

Ergot is derived from the fungus *Claviceps purpurea*.[3] Ergometrine is an ergot alkaloid, which when administered as ergometrine maleate or methylergometrine causes rapid tonic contraction of the uterus. It is therefore contraindicated for use in labour but is a second-line agent for postpartum haemorrhage (PPH) prevention.[3,4]

Ergometrine can be administered as an IMI or slow IVI at dosages of 0.1 to 0.5 mg. The onset of action is very rapid after IVI and within 1–5 minutes after IMI. It is metabolised by the liver and the half-life is 120 minutes.[3,4]

The exact mechanism of action is unclear but involves the influx of calcium into the myometrial cells. Proposed binding sites include calcium channels as well as α-receptors. Ergometrine also has an affinity for 5-hydroxytryptamine 1, noradrenaline, and dopamine receptors throughout the body.[1,3]

Side effects include systemic and pulmonary vasoconstriction and ergometrine is therefore contraindicated in preeclampsia, eclampsia, hypertension, and cardiac disease. A 0.5 mg dose results in a high incidence of nausea and vomiting.[3,4,6]

Syntometrine

Syntometrine is a 1 ml mixture of 0.5 mg ergometrine and 5 IU oxytocin. It is usually administered as IMI for the active management of the third stage of labour and the prevention of PPH, but may also be administered as a slow IVI for the management of severe PPH. The combination of the two drugs ensures a rapid onset of action and a sustained duration of action. The side effect profile is the same as for oxytocin and ergometrine and the contraindications are also the same.[1,3]

PGs

PGs are products of the arachidonic acid pathway and bind to their respective G-protein-coupled receptors. PGs E1, E3, F and T are thought to cause contractile responses, whereas PGs D, E2, E4 and I cause relaxation.[2]

The concentrations of PGF2α and PGE increase naturally during late pregnancy and enhance myometrial contraction, mainly by increasing the intracellular calcium concentration. PGF2α increases intracellular calcium by stimulating IP3-mediated SR calcium release, increasing the frequency of membrane action potentials and activating non-specific cation channels. The exact mechanism of PGE is unclear.[2]

Due to the very short half-life of the naturally occurring PGs, PG analogues were developed. Misoprostol, the synthetic analogue of PGE1, can be administered orally, sublingually, rectally, or vaginally. It does not need to be refrigerated during storage, unlike most other uterotonics. Misoprostol indications include termination of pregnancy, incomplete miscarriage, induction of labour (unfavourable cervix), and PPH. The PGs are more effective than oxytocin for the termination of pregnancy as the expression of OXTRs only increases during the third trimester.[1,2]

Dinoprostone, a PGE2 analogue, is usually administered as a gel to promote cervical ripening or to induce labour.[2,4] Intramyometrial PGF2α is a second-line agent for atonic PPH but is associated with severe side effects such as bronchospasm and ventilation-perfusion mismatch. IVI use is contraindicated. Other common side effects of synthetic PGs are hyperpyrexia, diarrhoea, nausea, and vomiting.[1,3,4,6]

Antiprogestins

Progesterone inhibits uterine contraction throughout pregnancy and maintains uterine quiescence (see tocolytics below). Antiprogestins, such as mifepristone, antagonise progesterone and indications include induction of labour and termination of pregnancy.[2]

Tocolytics

Once preterm labour is initiated, it progresses via the same mechanisms as term labour. Tocolysis aims to inhibit uterine contraction long enough for corticosteroid therapy to mature fetal lungs and improve neonatal outcomes. The many different drugs that have been used for the treatment of preterm labour include β2-adrenergic receptor agonists, calcium channel blockers, OXTR antagonists, magnesium sulphate (MgSO4), progesterone, PG synthesis inhibitors, and NO donors. None of these drugs seem to be effective in regularly prolonging pregnancy beyond 48 hours and there seems to be little consensus amongst international tocolytic guidelines as to which are the best tocolytics.[2,7,8]

Most of the current available tocolytic drugs were not specifically developed for tocolysis but for other indications and were found to have tocolytic side effects. Some of these drugs are used off-label as second-line tocolytics.[8]

β2-adrenergic receptor agonists

Drugs that belong to this group are salbutamol, terbutaline, ritodrine, and isoxsuprine.[2,4] They activate adenyl cyclase, thereby increasing cAMP and consequently protein kinase A (PKA). PKA regulates the phosphorylation and therefore inactivation of MLCK.[2]

Salbutamol is usually administered as a continuous intravenous infusion. Due to the wide distribution of β2-adrenergic receptors throughout the body, the side effects are extensive. They include tachycardia, palpitations, chest pain, dyspnoea, pulmonary oedema, hypokalaemia, hyperglycaemia, flushing, sweating, nervousness, tremors, nausea, and vomiting.[2,4]

Calcium channel blockers

Nifedipine blocks voltage-gated calcium channels and thereby prevents the influx of calcium into the myometrial cells. It seems to be more effective when used before 34 weeks of gestation and is usually administered orally. Maternal hypotension is the most common side effect and may be associated with placental hypoperfusion.[2,4]

OXTR antagonists

Atosiban is a competitive inhibitor of the OXTR as well as the vasopressin-1A receptor. Favourable results were initially shown with in vitro testing, but unfortunately, clinical effectiveness has not been demonstrated.[2]

MgSO4

Magnesium causes a dose-dependent reduction in intracellular calcium concentrations and thereby reduces the force of both spontaneous and oxytocin-induced uterine contractions. Magnesium antagonises calcium by reducing L-type calcium channel opening. Magnesium also possibly reduces intracellular calcium release from the SR. Another proposed mechanism is the reduction of PLC and hence IP3. Unfortunately, there is little clinical evidence that MgSO4 successfully prevents preterm labour. However, it may be useful in providing neuroprotection to premature infants.[2] Side effects of MgSO4 include hypotension, flushing, sweating, nausea, vomiting, blurred vision, headaches, palpitations, and decreased reflexes. It also has the potential to prolong the duration of action of neuromuscular blockers.[4]

Progesterone

Progesterone is a steroid hormone that is produced by placental tissue during pregnancy. It is pro-gestational and is thought to maintain uterine quiescence through the expression of genes associated with the contraction mechanisms of myometrial smooth muscle and by inhibiting the production of PGs. Progesterone also inhibits phosphodiesterase-4, which is responsible for cAMP inactivation. Furthermore, progesterone inhibits calcium influx and release from the SR and hyperpolarises cell membranes through the activation of potassium channels. It may also inhibit oxytocin binding.[2,7]

Progesterone can be administered orally, intramuscularly, and vaginally. Some evidence suggests that it sensitises the myometrium to other tocolytics, such as the β2-adrenergic receptor agonists, calcium channel blockers, and PG synthesis inhibitors, and that its main role may be to maintain tocolysis after the successful arrest of labour by other tocolytics.[2,7]

PG synthesis inhibitors

This group of drugs includes COX inhibitors, also known as nonsteroidal anti-inflammatory drugs (NSAIDs). The tocolytic effects of both non-specific COX and COX-2-specific inhibitors have been studied. NSAIDs prevent the breakdown of arachidonic acid into the various PG isoforms.[2]

During labour, the production of PGs and COX-2 increases in the fetal membranes and the myometrium.[9] Inhibition of COX therefore reduces the production of PGs and thereby reduces myometrial contraction.[2,9] Unfortunately clinical trials have not shown a significant reduction in the incidence of preterm labour with either indomethacin or selective COX-2 inhibitors.[2] The COX-2 inhibitors have also been associated with severe fetal and neonatal side effects, such as impaired renal function, oligohydramnios, necrotising enterocolitis, and intraventricular haemorrhage. Gastrointestinal side effects are common in mothers. Due to the risk of premature closure of the ductus arteriosus, NSAIDs should only be administered for short periods before 32 weeks of gestation.[2,4]

NO donors

NO activates guanyl cyclase and therefore increases the production of cGMP and protein kinase G (PKG). PKG inhibits calcium influx. Unfortunately, several randomised controlled trials have shown that nitroglycerin does not delay labour or improve neonatal outcomes.[2] Hypotension, headache, and platelet dysfunction are some of the side effects.[4]

Novel tocolytics

2-aminoethoxydiphenyl borate (2-APB), glycyl-H-1152 dihydrochloride (GH), and HC-067047 are currently being investigated as novel tocolytics. 2-APB is an IP3 receptor inhibitor and blocks various routes of calcium influx into the myometrium. GH is a selective inhibitor of rho-kinase, which plays a role in the phosphorylation of myosin light chains. HC-067047 is an inhibitor of TRPV4, a non-selective cation channel involved in calcium influx.[8]

Volatile anaesthetic agents

Halothane, isoflurane, sevoflurane, and desflurane all decrease myometrial contractility in in vitro studies. The inhibitory potency of halothane, sevoflurane, and desflurane seems to be similar and possibly greater than that of isoflurane. At less than one minimum alveolar concentration, oxytocin can re-establish uterine contractility reduced by the volatile anaesthetic agents.[10]

The underlying mechanism of volatile-induced myometrial relaxation is unclear. Inhibition of various potassium channels and L-type calcium channels as well as changes to myofilament calcium sensitivity have been proposed.[10]

The effects of propofol and dexmedetomidine on the myometrium

In vitro and in vivo animal studies have demonstrated that propofol reduces oxytocin-induced myometrial contraction and dexmedetomidine increases it. The underlying mechanisms are unclear.[11]

ORCID

T Kleyenstuber https://orcid.org/0000-0001-5219-3869

References

1. Gizzo S, Patrelli TS, Gangi SD, et al. Which uterotonic is better to prevent the postpartum hemorrhage? Latest news in terms of clinical efficacy, side effects, and contraindications: a systematic review. Reprod Sci. 2013;20(9):1011-9. https://doi.org/10.1177/1933719112468951.
2. Arrowsmith S, Kendrick A, Wray S. Drugs acting on the pregnant uterus. Obstet Gynaecol Reprod Med. 2010;20(8):241-7. https://doi.org/10.1016/j.ogrm.2010.05.001.
3. Dyer RA, van Dyk D, Dresner A. The use of uterotonic drugs during caesarean section. Int J Obstet Anesth. 2010;19(3):313-9. https://doi.org/10.1016/j.ijoa.2010.04.011.
4. Diedericks BJS, Brandl AB. Smooth muscle agents. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 1st ed. Centurion: MedPharm Publications; 2012. p. 321-7.
5. Fitzgerald PA, Klonoff DC. Endocrine drugs. In: Katzung BG, editor. Basic clinical pharmacology. 7th ed. Connecticut: Appleton & Lange; 1998. p. 603-18.
6. Farina Z, Fawcus S. Oxytocin-ensuring appropriate use and balancing efficacy with safety. S Afr Med J. 2015;105(4):271-4. https://doi.org/10.7196/SAMJ.9179.
7. Navathe R, Berghella V. Progesterone as a tocolytic agent for preterm labor: a systematic review. Curr Opin Obstet Gynecol. 2016;28(6):464-9. https://doi.org/10.1097/GCO.0000000000000327.
8. Hossain MR, Tolosa JM, Young RC, Smith R, Paul JW. Assessing the potency of the novel tocolytics 2-APB, glycyl-H-1152, and HC-067047 in pregnant human myometrium. Reprod Sci. 2023;30(1):203-20. https://doi.org/10.1007/s43032-022-01000-2.
9. Sawdy RJ, Sullivan MHF, Bennett PR. The effects of non-steroidal anti-inflammatory compounds on human myometrial contractility. Eur J Obstet Gynecol Reprod Biol. 2003;109(1):33-40. https://doi.org/10.1016/S0301-2115(02)00481-5.
10. Yoo KY, Lee JC, Yoon MH, et al. The effects of volatile anesthetics on spontaneous contractility of isolated human pregnant uterine muscle: a comparison among sevoflurane, desflurane, isoflurane, and halothane. Anesth Analg. 2006;103(2):443-7. https://doi.org/10.1213/01.ane.0000236785.17606.58.
11. Kimizuka M, Tokinaga Y, Azumaguchi R, et al. Effects of anesthetic agents on contractions of the pregnant rat myometrium in vivo and in vitro. J Anesth. 2021;35(1):68-80. https://doi.org/10.1007/s00540-020-02866-9.