The autonomic innervation of the uterus

A short review on pharmacological aspects

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Abstract

Despite the important volume of data regarding the physiology and pharmacology of uterine smooth muscle innervation, it is unclear the precise role of the nervous supply on myometrial activity. Moreover, although all uterine myocytes possess specific adrenergic and cholinergic receptors, the autonomic fibers are almost exclusively distributed to cervix (eventually to isthmus, which becomes the lower uterine segment in the last part of the pregnancy), where is located less that 10% of the whole myometrium. It seems that neuronal modulation is implicated more on cervical dynamics and poorly on "effective" uterine contractility. It is important to note that constantly there is a neuronal co-transmission, either sympathetic or parasympathetic, or even non-adrenergic/non-cholinergic mediation, the number of discovered compounds, able to modulate the uterine activity, increasing permanently. Must be mentioned, also, the variability of receptors either as density, sensitivity or intracellular pathways, depending of hormonal impregnation, especially on gestation. Furthermore, during pregnancy, placenta and amniotic membranes possess a strong impact on myometrium, connective tissue, but also on neuronal ending characteristics.
Keywords: *sympathetic, parasympathetic, co-transmission, non-adrenergic non-cholinergic*

Introduction

Although there is enough information about both morphological and pharmacological characteristics of uterine autonomic nervous supply, the precise importance of the neurological component on uterine modulation, remains to be determined.

The autonomic nervous fibers, distributed to the uterus, release noradrenaline (from sympathetic endings), acetylcholine (from parasympathetic fibers), but also a great number of other compounds, which, beside the two main neurotransmitters, can modulate myometrial activity.

It must be mentioned the strong hormonal dependence of the local specific receptors for almost all neuromediators, either as type (or subtype), density, sensitivity or intracellular signalling pathways.

Furthermore, the association of placenta and amniotic membranes during pregnancy, modify, supplementary, not only the myometrial sensitivity to local neurotransmitters, but also the regional nervous fibers either as density or mediators release.

The labor progression and the autonomic nervous supply. A continuous positive cycle

The progression of the fetus through the genital channel causes distension of the lower segment and, especially, of the cervix. Excitation of the local nerve endings induces (at least theoretically) hypotalamic oxytocin release, with increased uterine activity (Fergusson reflex).

Moreover, also through a cervical reflex mechanism, it is stimulated the release of neuromediators from periuterine nerve endings, with contractile effects. In the same time, the exocytosis of secretoneurin from the same nerve endings (also induced by local tissue distention), leads to local increased density of leukocytes, particularly macrophages, cells with important roles on cervical dynamics[(1)].

As labor progresses, the distension of the vagina, uterine ligaments and surrounding organs, also by reflex mechanism, accelerates myometrial contractility.

A fundamental role also plays the rectal distension, which, in addition to inducing ejection reflex (abdominal press is especially important for fetal expulsion), stimulates uterine contractility and, especially, accelerates cervix effacement and dilation. The histochemical identification could support this clinical observation of particular autonomic nerves, which make a direct reflex arc rectum-marrow-cervix[(2)].

Even distension or dissociation of the perineal various somatic components, either directly[(3)] or indirectly, through intense pain sensation, accelerate the uterine contractility[(4)].

In the same time, all these phenomenons, occurring in response to the involvement of various structures during fetal progression, are accompanied by local hemodynamic changes, appropriates for the purposes of enhancing irrigation in the utero-vaginal area[(3)].

General pharmacological aspects on uterine autonomic innervation

Uterine innervation has two components:

- one afferent, interoceptiv type, which is responsible for transmitting information to the central nervous system (this component is not an issue for this paper) *and*
- efferent, autonomic type.

It is important to note that in myometrium (as in other types of smooth muscle) there is neither direct

contact between axonal endings and myocytes, nor specialized structures, synapses, the neurotransmitter being released (by exocytosis) in the perifascicular space, stimulating different receptors, situated on the muscular cells membrane. It is however, some limitation of the area in which the neural discharge takes place, the so-called „diffuse synapses"[5].

Knowing that axonal branches finish in the matrix surrounding muscle bundles, it is clear that only smooth fibers located on the outside may be directly stimulated by neurotransmitters. The inside cells (which has no innervation) will be stimulated indirectly by action potentials from outer fibers, especially through "gap" junctions.

Typically, axonal endings in smooth muscle, all unmyelinated, present numerous varicosities, where there are stored the specific neurotransmitters for each type of autonomous innervation[5] (figure 1). The containing active substances are released, by exocytosis, either following the arrival of an impulse along the axon or spontaneously.

Uterine innervation is strongly dependent, both morphologically and functionally, on the hormonal impregnation. Paradoxically, however, unlike the actions on the myometrium, estrogens inhibit the development of uterine innervation, the sympathetic system being far more affected. This can be demonstrated in experimental conditions, when estrogens are used at high doses during animal growth[6].

In clinic, during normal pregnancy (in conditions of extremely high estrogen concentrations), there is a gradual decrease in the ratio between the number of nervous fibers and muscle bundles[6]. (Note that, however, the number of both structures significantly increase, in real value, during pregnancy). This phenomenon may contribute to the continuous decrease of the myometrium activity until term, despite the very marked amplification of its contractile capacity, resulting from its strong hypertrophy.

It was also noted that other particular circumstances may influence uterine innervation:

- adenomyosis (the presence of endometrial tissue in uterine muscle) is accompanied by reduction up to disappearance of nerve endings around the lesion[7];
- inflammatory pelvic diseases, by contrast, increase neural density terminals intra and periuterine[7], being a cause of the intense pain, which accompany, cvasipermanent, this gynecological pathology.

Classically, there are two types of autonomic innervation:

- adrenergic or sympathetic, which is the most important[4], *and*
- cholinergic or parasympathetic.

In reality, however, autonomic innervation is far more complex, involving almost constantly, several types of co-transmission, even non-adrenergic/non-colinergic fibers (see below).

Regardless of type, the autonomic efferent pathway is consisting from two neurons, the first located in the side horn of the spinal cord, and the second in vegetative ganglia.

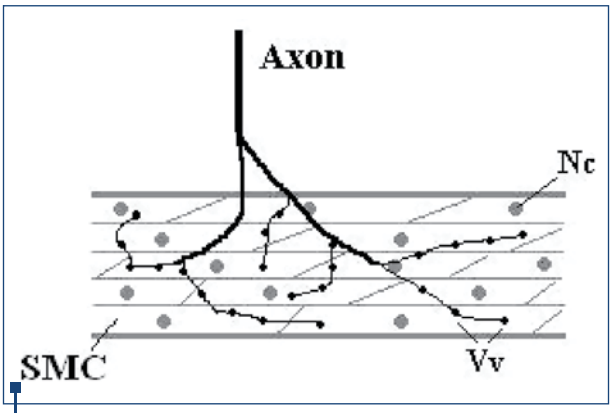

Figure 1. The scheme of the innervation of a uterine smooth muscle bundle. (SMC = Smooth muscle cell; Nc = Nucleus; Vv = Varicosities)

Sympathetic or adrenergic innervation

Autonomic uterine innervation is largely of sympathetic type[4]. Sympathetic fibers, represented by the axons of postganglionic neurons, have their origins in paraspinal ganglia tail-10-lumbar 1. Axonal endings, that reach the uterus, are distributed throughout the musculature, especially the cervical area.

Terminal knobs, belonging to final sympathetic ramifications, contain vesicles with: noradrenaline (responsible for the adrenergic effects), dopamine β-hydroxylase (the enzyme that converts dopamine to noradrenaline), adenosine triphosphate (ATP), cromogranin and other proteins.

Noradrenaline intensely stimulates α_1 receptors, more poorly the α_2 and β_1 receptors[8], β_2 effects being reduced[9].

Uterine muscle cells, belonging to circular bundles (so in the cervico-isthmic area), possess, especially, type α1 adrenergic receptors (α_{1A}), with contractil effect, while those from the uterine body, mainly possess β_2 adrenergic receptors, which induce tocolysis (table 1).

Despite the lower number of α_1 receptors face to β_2 in uterine muscle (situated mainly in the uterine body), because the low affinity of noradrenaline for β_2 receptors, this catecholamine induces contraction, both *in vivo* and *in vitro*, regardless of the uterine region. Even during pregnancy when there is a marked increase in the ratio β_2/α_1 receptors (this contributing to the uterine hipocontractility, absolutely required to maintain pregnancy), noradrenaline maintains ocytocic action.

So, automatically, the sympathetic nervous system stimulation, where nordarenaline is the main mediator, will lead, invariably, to ocytocic effect.

It is important to note that in the last weeks of pregnancy occurs a desensitization of β_2 receptors, being possible that this phenomenon contribute to the initiating of the labor to term[10]. In the same direction comes the observation that the number of α_1 receptors increases linearly until term[11] (but still well below the β_2), which, associated to β_2 receptor desensitization, could contribute to labor induction.

On the uterine smooth muscle cell membrane there were also identified α_2 receptors, including all their

Table 1 The main neurotransmitters contained in the varicosities of uterine nervous endings, their specific receptors on myometrial smooth muscle cells, intracellular signaling pathways involved and their effects on uterine contraction

Neuromediator	Uterine smooth muscle cells receptors			Intracellular signaling pathways activated	Effects on myometrium
NOR-ADRENALINE	α	α_{1A}		**PLC/PIP_2/IP_3/DAG/Ca^{2+}**[5] PLA_2/AHA/PG (leukotrienes) AC (-) ⟶ cAMP (-) L-calcium channels (+) ⟶ [Ca^{2+}]i (+)	**Contraction** Contraction Contraction Contraction
		α_{2A} (α_{2B}, α_{2C})	„Post-synaptic"	**PLC/PIP_2/IP_3/DAG/Ca^{2+}**[26] AC (-) ⟶ AMPc (-)[27]	Contraction Contraction
			„Pre-synap-tic"[5]	AC (-) ⟶ cAMP (-) K^+ channels (+) L-calcium channels (-) ⟶ [Ca^{2+}]i (-)	All decrease the norepinephrine release from simpathetic endings
	β	β_2		**AC (+) ⟶ AMPc (+)**	**Tocolysis** Antimitogen effect[28]
				Ca^{2+}- sensitive K^+ channels (+)[12] ATP - sensitive K^+ channels (+)[29]	Tocolysis Tocolysis
		β_1, β_3[9,14]		AC (+) ⟶ cAMP (+)	Tocolysis
ACETYLCHOLINE	**M**	**M_3**		**PLC/PIP_2/IP_3/DAG/Ca^{2+}** Ca^{2+}- sensitive K^+ channels (+)[12] ATP - sensitive K^+ channels (+)[30]	**Contraction** Contraction Contraction
		M_2		AC (-) ⟶ cAMP (-)[16]	Contraction
ATP	P1 (A)	A1[19]		Only during pregnancy AC (-) ⟶ cAMP (-)	Contraction[31]
				Only on non-pregnant uterus PLC/PIP_2/IP_3/DAG/Ca^{2+}	Contraction[31]
	P2	**$P2_{y2}$**[32]		**PLC/PIP_2/IP_3/DAG/ Ca^{2+}**[33] PLA_2/AHA/PG (leukotrienes)[32]	Contraction[12,32]
		$P2_{x4}$[34] ($P2_{x1}$'2,3,5,6,7)		[Ca^{2+}]i (+)	Contraction
Tachykinins	SP	**NK_2 - NKA > SP**[21,35,36]		PLC/PIP_2/IP_3/DAG/Ca^{2+}[37]	Contraction[25]
	NKA	NK_1 - SP > NKA NK3 - NKA > SP		PLC/PIP_2/IP_3/DAG/Ca^{2+}[21]	?
NPY		$Y1$[38]		**AC (-)⟶ AMPc (-)**[7] PLC/PIP_2/IP_3/DAG/Ca^{2+}	Contraction[39]
Galanin		$GAL\text{-}R_1$		PLC/PIP_2/IP_3/DAG/Ca^{2+}	Contraction
Gastric releasing peptide (Bombesin)		GPCR[40]		PLC/PIP_2/IP_3/DAG/Ca^{2+}[40]	Contraction[41]
CCRP		**CGRP-B** CGRP-A Their density increases during pregnancy and decrease near term[42,43,44]		**Ca^{2+}-sensitive K^+ channels (+)**[45] ATP - sensitive K^+ channels (+)[46]	Tocolysis (Possibly it contributes to the specific uterine „hipontractility" during pregnancy. This action is decreasing to term.)

VIP		**VIP-1** VIP-2	GPCR ?[47]	AC (+) → cAMP (+)[3,47]	Tocolysis[47]
ANP		**ANP-A** ANP-B Their density decreases during pregnancy term[48]		**cGMP (+) → PKG (+)**[49]	Tocolysis[50]
NO		**GC**[20]		**GC (+) → cGMP (+)**	Tocolysis
		Ca^{2+} - sensitive K^+ channels (+)[12,51]			Tocolysis
		ATP - sensitive K^+ channels (+)[22]			Tocolysis
		The sensibility increases during the second part of the pregnancy and decreases rapidly near term and especially in labor. (Any contribution to the physiological uterine characteristics during pregnancy?)[52]			
Opioids	**END**	Exist only during pregnancy[53]	**μ END>ENK**	?	No proven effect on myometrial smooth muscle cells. Different effects on local neurons, placenta, amnionic membranes, connective cells etc.
	ENK		k ENK>END		
Dopamine		No receptors[12]		---	Different effects on local neurons, endometrium, placenta, connective cells etc.
Colecistokinin		?		?	?
Somatostatin		?		?	?

(PLC = Phospholipase C; PIP_2 = Phosphatidilinositol 4,5-bisphosphate[4,5] IP_3 = Inositol triphosphate[1,4,5]; DAG = diacylglycerol; PLA_2 = phospholipase A_2; AHA = arachidonic acid; cGMP= cyclic guanosine monophosphate; PGs = prostaglandins; AC = adenylyl cyclase; cAMP = cyclic adenosine monophosphate; P_2= purinergic receptor 2; $[Ca^{2+}]i$ = intracellular calcium; SP = substance P; NKA = Neurokinin A; NK_2= neurokinin receptor 2; NPY = neuropeptide Y; GPCR = G Protein-coupled Receptor; CGRP= calcitonin gene-related peptide; ANP= atrial natriuretic peptide; VIP= vasoactive intestinal peptide; GC = guanylyl cyclase; PKG = protein kinase G; NO= nitric oxide; END= endorphins; ENK= enkephalins); (The bolded and colored data are considered the most important, [1] marks the corresponding reference)

subtypes: A, B, C (predominantly α_{2A}; 12), also with contractile effect[12] (table 1). Unlike α_1 receptors, after a linear increase during pregnancy, there is a marked desensitization of the α_2 receptors within birth[11].

α_2 adrenergic receptors can be located on the uterine myocyte membrane ("postsynaptic") but, more importantly, on the sympathetic nerve endings membranes, ("presynaptic"), inhibiting the catecholamines release from the adrenergic fibers[13].

In the same time, myometrial cells possess β_1[14] and β_3 receptors[13], both with tocolytic effect (through the same mechanisms as β_2 receptors) (table 1).

But the biological impact of α_2, β_1 and β_3 receptors, on the modulation of uterine contractility, remains to be decided.

There have been identified, in the periuterine area, adrenergic nerve fibers that secrete dopamine[15]. Myometrium does not have specific receptors for this catecholamine, but dopamine is able to interact with other uterine structures: nervous endings, endometrium, respectively, in pregnancy, decidua or placenta.

Parasympathetic or cholinergic innervation

Parasympathetic postganglionic fibers, which have their origin in the inferior hypogastric ganglion, are distributed almost exclusively in the cervix. Cholinergic endings possess vesicles that contain acetylcholine, stored together with ATP, proteoglycans and other proteins. Acetylcholine stimulates specific membrane receptors (muscarinic receptors, M_{1-5} and nicotinic receptors, NN,M), on uterine myocytes existing only two muscarinic receptor subtypes: M_2 and M_3[13,16].

In vitro, acetylcholine administration induces an increase in frequency and intensity of myometrial contractile waves, without a significant change in tone (phasic type effect).

Ocytocic action of acetylcholine is mainly due to M_3 receptor stimulation, located on the myometrial smooth muscle cells membrane (table 1).

Although M_3 receptors are present on the membrane of all myometrial cells, cholinergic endings are distributed only to the cervical area and isthmus and only in small numbers in the rest of the uterus. So, the parasympathetic stimulation causes cervical fibers contraction, less isthmic area muscle contraction (isthmus corresponds to the low segment, in late gestation), with little, or no effect on the uterine body. The contraction of the circular muscle bundles of the cervix, during pregnancy, has a content effect, preventing the

premature rupture of membranes and, hence, the early expulsion of the fetus.

Neuronal autonomic co-transmission

It is known that in the final button vesicles, belonging to both adrenergic and cholinergic endings, alongside with classical mediators: noradrenaline, and acetylcholine, respectively it is a whole range of other substances able to modulate smooth muscle cell activity. They realize the so-called phenomenon of "co-transmission", which is more frequent and more intense on parasympathetic fibers.

Moreover, it was found that the postganglionic neurons, both sympathetic and parasympathetic, if they are in culture, in the absence of physiological nerve stimulation (which normally is done by acetylcholine), released mainly, sometimes exclusively, other mediators[17].

Another feature is that, frequently, there are involved neurotransmitters with opposite effects, contractile and relaxing.

Sympathetic co-transmission

Noradrenaline is released from the sympathetic neurons, through exocytosis, together with ATP, cromogranin, dopamine β-hydroxylase and other compounds (Hoffman and Lefkowitz, 2001).

ATP has, itself, uterine contractil effect (table 1).

Adrenergic vesicles contain also, different substances with:

- ocytocic effect[18,19,20,21]: tahikinins (SP), the most important and NKA, NPY and galanin;
- tocolytic effect: CGRP, ANP;[22] and NO[19].

Also can be released somatostatin[18], but its role on uterine modulation is uncertain.

Moreover, there are adrenergic endings that generate co-transmission noradrenaline/acetylcholine[23].

Parasympathetic co-transmission

Among the parasympathetic endings, acetylcholine is removed from the vesicles, together with ATP, proteoglycans and other compunds[17,18,19,24], with:

- ocytocic effect: ATP, NPY or
- tocolytic effect: CGRP, VIP and NO (table 1).

Parasympathetic endings can also contain endogenous opioids (endorphines and enkephalins), for which the myometrium has specific receptors, but their role in shaping the uterine contraction, if any, is very low. These substances, however, decrease the release of neurotransmitters from local nerve endings and also can interact with specific receptors, located on the membrane of connective tissue cells, endometrium, placenta etc.

Non-adrenergic/non-cholinergic autonomic innervation

There are nerve endings, belonging to the autonomic nervous system, which release neither noradrenaline nor acetylcholine. These are the so-called nerves:

- peptidergic, which secrete exclusively one or more peptides: SP, cholecystokinin, VIP, galanin, bombesin, CGRP[18,19,25] or
- purinergic, having as sole mediator ATP[20].

There are also, axonal endings that secrete dynorphins or enkefalins[19] (generally, in combination with other peptides or ATP) or NO (also, alone or with other mediators)[18,19].

Most non-adrenergic/non-cholinergic nerves are present in the digestive tract, but exist, also, in genitourinary tract.

An important feature is that the non-adrenergic/non-cholinergic fibers act as sensitive and effectory fibers in the same time. Therefore, the stimulation of their endings cause the reflex release of the compounds contained in the same endings or other endings, belonging to the same axons[26]. ■

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