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# Functioning of oxytocin receptor in the central nervous system and smooth muscles

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*Investigation of the mechanism of neuronal communication underlies the fundamental discoveries that promote health. The studies of oxytocin signaling in neurons from or within different brain areas are directed to explore the role of this neurohormonal modulator in the regulation of synaptic transmission and plasticity, neuronal excitability that contributes to the reproduction, social behavior and learning capacity, anxiety, inflammation and differentiation in the brain. Oxytocin is synthesized in supraoptic and paraventricular nuclei of the hypothalamus and when secreted into the bloodstream from the posterior pituitary, it produces a significant effect on uterine contraction and lactation. At the same time this nonapeptide being released within the limbic system and brain cortex modulates neuronal activity by affecting ion channels on their membranes. The oxytocin receptor is primarily coupled to Gq/11 proteins causing phospholipase C activation, $Ca^{2+}$ release and store-operated $Ca^{2+}$ entry. These pathways are central for the regulation of the activity of different types of TRP channels, especially of the canonical subfamily (TRPC). Here we highlight the link between oxytocin signaling, which is particularly well investigated in the myometrium, and receptor-operated TRPC4 and multimodal TRPV4 ion channels that participate in oxytocin-dependent regulation of the uterine smooth muscle contractility under various conditions. Importantly, similarly to oxytocin, these channels have been implicated in neuropathic pain behavior, anxiety, fear and depression. Since similar signal transduction pathways are likely to be functional in neuronal cells, we propose that future studies of oxytocin effects in the CNS should also consider the role of these $Ca^{2+}$-permeable channels.*
*Keywords: oxytocin, neurons, brain, uterine smooth muscle, ion channels*

## INTRODUCTION

Society of Neuroscience has defined core concepts of modern Neuroscience among which we can find #2 (Neurons communicate using both electrical and chemical signals) and #8 (Fundamental discoveries promote healthy living and treatment of disease). Thus, investigation of the particular cellular and molecular mechanisms of neuronal functioning, regulation and communication via electrical and chemical signals underlies the fundamental discoveries that promote health.

Oxytocin (OT) is among WHO approved and recommended agents to induce labor and to prevent postpartum hemorrhages [1]. Thus, it is administered in levels exceeding the physiological level and considering its powerful action in the brain we have to clearly define the effect of OT on the functioning of neurons. Although the prevailing view is that OT cannot cross the blood-brain barrier [2–4], the effect of OT on smooth muscle can be useful to understand also the effects on neurons but with certain strengths and limitations. By binding to the oxytocin receptors (OTR), OT mediates a variety of effects in the brain including maternal behavior and mother-infant recognition, social reactions, stress response and food intake, modulation of the visceral vagal regulation and also neocortex development and growth, brain blood supply and maintenances the healthy brain environment via its antioxidant and anti-inflammatory cellular effects [5,6].

Investigation of OT signaling in the brain requires complicated experimental approaches

including neuronal cell culture [7], fresh cell isolation [8], stereotaxic surgery [9], and bioinformatics methods [10]. We believe these approaches may be greatly complemented and even extended with the techniques used in visceral smooth muscle research for the determination of particular regulatory messengers or effector molecules in the intracellular signaling pathways. This indeed may be a rational approach to the problem since numerous studies illustrate the fact that communication between similar sets of molecular components if these are present in different cell types, may be highly similar in the initial signal transduction, while functional outcomes (secretion, contraction, action potential discharge, etc.) are of course cell type specific. Certainly, it is easier to record and interpret smooth muscle contractility compared to much more complex brain functions, especially if we choose a tissue that abundantly expressed OT receptors.

**Oxytocin synthesis and release**

OT is synthesized in magnocellular neurons of the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei. These neurons in vertebrates originate from the wall of the third ventricle, migrate and transform from bipolar into the cells with reach dendrite tree and bifurcated axon that allows extra pituitary release of OT, in the forebrain in particular [11]. OT release from axonal terminals within the posterior pituitary delivers the peptide into the bloodstream and release from the neuron dendrites contributes to the brain pool of this peptide [12]. OT being delivered in the latter way dramatically increases the local concentration of OT comparatively to the serum level and this elevation together with the localization of OT-releasing nuclei near the third cerebral ventricle facilitates the brain distribution of OT.

$Ca^{2+}$ channels are found to be critical for the differential release of OT and for the control of firing patterns of the OT-releasing SON neurons [13]. Dendritic release of the OT requires $Ca^{2+}$ entry that may be modulated by GABAA receptors on dendrites [12]. Various signals act via different amounts of this calcium.

**Receptors for oxytocin and their signaling**

To elicit its effect in the brain, OT binds with OTR or in some cases (at high concentration or in the absence of OTR) with the related vasopressin receptors V1a, V1b and V2 [11] with the preference of V1a receptors when specific social behavior is modulated [14–16]. OTR expression in the uterus and the brain is estrogen-dependent [17,18].

Interaction of OT with the binding site on the receptor triggers the G-protein cascade transmitting the signal further via second messengers [19] (Fig. 1).

Most effects of OT are mediated via Gq/11 signaling cascades but some evidence has been obtained about the Gi/o pathway involved. It is not clear yet if there is a kind of switching between Gq/11 - Gi/o coupling after OTR binds the ligand but the kind of a promiscuous coupling has been reported [20]. In CA2 pyramidal neurons Gq/11 coupled OTR causes inhibition of the outward currents by phosphatidylinositol 4,5-bisphosphate (PIP2)-dependent closing of inward rectifying potassium channels (Kir) and the hyperpolarization-activated cyclic-nucleotide-gated (HCN) channels that leads to the increase of the cell excitability [21] but there are data demonstrating participation of Gi/o subtype in the OT response of these cells [22]. There is evidence that OT when binds with the Gq/11 coupled V1A receptors, may engage calcineurin pathways to dephosphorylate acid-sensitive chloride channels (ASIC3) decreasing the current amplitude in primary sensory neurons [8].

OT appeared to be unable to induce OTR-Gs activation in neurons [23]. Gβγ uncoupled from Gq/11 mediates the burst onset in the SON neurons in response to OT [24].

In visceral tissues, namely in the uterus where OTRs are expressed on myometrium cells, Gq/11 alpha subunit activates phospholipase C (PLC) resulting in diacylglycerol and inositol-1,4,5-trisphosphate ($IP_3$) formation that

activates protein kinase C and liberates stored calcium, respectively [25]. Pathways mediated by PKC and $Ca^{2+}$ underlie oxytocin regulation of the vascular tone when the endothelium cells start to produce nitric oxide (NO) [19]. The increase of intracellular $Ca^{2+}$ also involves store-operated (capacitative) $Ca^{2+}$ entry as a part of the uterotonic effect of OT that engages nonselective cation channels (known as SOC or CRAC channels) [19]. Increased intracellular $Ca^{2+}$ in myometrium also triggers the calcineurin/NFAT signaling pathway, where dephosphorylation of nuclear factor of activated T cells (NFAT) leads to NFAT translocation to the nucleus and activation of the genes, engaged in the labor onset. Nuclear localization of NFAT mirrors the periodic release of OT, with the frequency of these nuclear translocations dependent on the pulsatile secretion of OT [26].

In primary human myometrium cells activated OTR also triggers ERK1/2 phosphorylation via Gβγ uncoupled from Gq/11 [26]. OTR-Gi/o pathway in human prostate cancer cells modulates cell migration and metastasis development [28]. This signal cascade via a decrease in cAMP level also mediates the inhibition of HEK293 cells and the facilitation of the inwardly rectifying K+ current in certain sub-populations of GN11 cells [29]. OT-dependent phosphorylation of mitogen-activated protein kinase (MAPK) was described in cultured human myometrium cells as one more signaling pathway [19]. OT also facilitates contractility by activation of RhoA–Rho-kinase cascade that inhibits myosin phosphatase thus inducing calcium sensitization [30].

Thus, after binding with a single OTR and/or related V1 vasopressin receptor, OT realizes its effect via several G-protein mediated pathways and mostly results in the intracellular $Ca^{2+}$ increase and protein phosphorylation by various kinases. There are many intricate questions

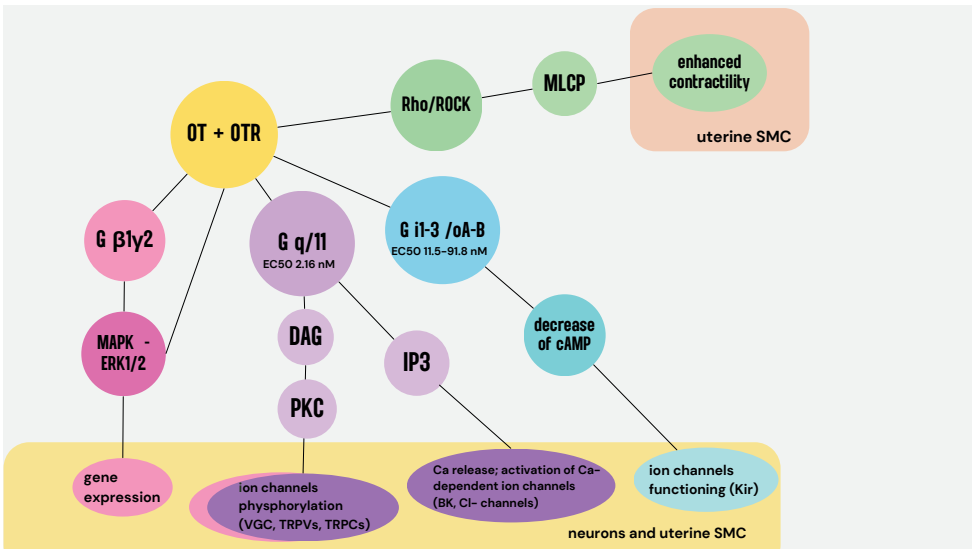


Fig.1. Intracellular pathways involved in the OT-OTR signaling include some common elements for neurons and visceral smooth muscles (Gq/11 and Gβγ mediated activation of protein kinases that phosphorylate ion channels changing their functional state and $Ca^{2+}$-dependent activation of ion channels). The distinct element, typical to uterine SMC, is the Rho/ROCK mediated phosphorylation of MLCP that facilitates contractility. $BK_{Ca}$ – $Ca^{2+}$-activated potassium channels of large conductance, cAMP – cyclic adenosine monophosphate, ERK1/2 - extracellular signal-regulated kinase types 1 and 2, IP3 – inositol 1,4,5-trisphosphate, Kir – inwardly-rectifying potassium channels, MAPK – mitogen-activated protein kinase, MLCP – myosin light chain phosphatase, OT – oxytocin, OTR – oxytocin receptor, PKC – protein kinase C, ROCK – Rho-associated protein kinase, DAG – diacylglycerol, TRPVs – transient receptor potential channels of vanilloid subfamily, TRRCs – transient receptor potential channels of canonical subfamily, VGCC – voltage-gated calcium channels.

regarding a possible multimerization of OTRs, the specificity of receptor coupling to different types of G-proteins, the roles of Gβγ subunits, etc., which are currently being investigated with the aim of achieving a better understanding of the complex neurophysiology of the OT signaling, including the problem of exactly how this single neurohormone can regulate so many different cellular functions and in so many different types of cells. These questions (which are largely outside the scope of this paper) have recently been reviewed elsewhere [11,22,29]. Of most relevance to our following discussion of future perspectives are the important findings that are now emerging from studies of OT signaling outside of the CNS, for example in the vasculature [30]. In this context, there is also emerging evidence for co-localization of OTRs and TRP channels in the brain, suggested to be of importance for neuroendocrine regulation (e.g., TRPV5, TRPV1) [31,32].

Perspective – how the investigation of ion channels engaged in oxytocin pathways in smooth muscle tissue may contribute to neurophysiological research

**Ion channels engaged by OT in neurons are similar to those in viscera**

OT via OTR or V1 receptors engages ion channels as the end effector molecules in signaling cascades and these ion channel subtypes are highly similar in the brain and visceral tissues. For instance, dorsal root ganglion (DRG) neurons develop OT-evoked hyperpolarization mediated by outward currents via ATP-sensitive $K^+$ channels activated by $Ca^{2+}$-stimulated NO synthesis [33]. A similar mechanism has been described in the jejunum sensory neurons [34]. OT-induced analgesic effects in trigeminal neurons in experiments on TRPV1-knockout mice and planar lipid bilayers with TRPV1 incorporated are based on their desensitization [35]. In various hippocampal neurons, OT mediates its effect via PKC-dependent phosphorylation of voltage-gated L-type $Ca^{2+}$ and $Na^+$ channels as well as P/Q-type calcium $Ca^{2+}$ channels and Kv7 channels [37]. Some of these channels are also associated with the OT signaling in visceral smooth muscles [25].

**The role of TRP ion channels recruited by OT in smooth muscles may be quite similar in neurons**

The acute behavioral effect of oxytocin is based on the increased intracellular $Ca^{2+}$ level. In hypothalamic neurons, this is achieved via the activation of TRPC3 and TRPV1-6 channels. The TRPV2-mediated OT-activated $Ca^{2+}$ increase in PVN neurons involves phosphoinositide-3 kinase (PI3K) and/or leads to the activation of mitogen-activated protein kinase (MEK1/2) [38]. OT-induced depolarization of the subiculum neurons appeared to mediated by PKC- but not store-dependent engagement of TRPV1 [33].

In the uterus, OT together with TRPV1 are involved in the pathogenesis of dysmenorrhea, but the relationship between the hormone and the channel activity has hardly been observed [38]. Some other visceral tissues express TRPV1, but their effect on smooth muscles is often indirect [39].

TRPV4 are found to be one of the end molecular targets in the oxytocin intracellular pathways in visceral and vascular smooth muscles that affect myocytes excitability and/or contractility [40–42]. In murine myometrium strips, TRPV4, when activated, leads to $Ca^{2+}$ entry and contraction development and appears to mediate oxytocin-induced contractile response that was diminished under TRPV4 global deletion [43]. On the other hand, inhibitory effect of TRPV4 stimulation by 100 nM of its selective agonist GSK1016790A had been demonstrated, but it was mediated by other cells and transmitters so can also be indirect to smooth muscle cells [44]. A similar response has been observed in uterine myocytes, where these channels contribute to the local $Ca^{2+}$ increase that triggers activation of $BK_{Ca}$ channels thus causing membrane hyperpolarization [41] highlighting the role of TRPV4 channels as a limiting factor for OT-stimulated contractility. Our experiments on isolated human myometrium samples taken from patients at the term of labor demonstrated that TRPV4

selective antagonist HC067047 (1 μmol/l) in the presence of oxytocin (10 nmol/l) in one group of human strips (n=4) enhanced contractions up to 31% in some strips (Fig. 1a, 1a). At the same time in another group of muscle strips (n=4) TRPV4 blockade attenuated phasic contractions and inhibited OT-stimulated contractions (Fig. 2c, 2d).

In smooth muscle cells, TRPV4 mediated $Ca^{2+}$ entry activates several mechanisms depending on the colocalized ion channels / regulatory proteins and participates in OT signaling as described above. Thus, in neurons, TRPV4 activation may also be involved as the end target in the OT cascade. The only reported case is that TRPV4 and regulation of its expression in sensory neurons of the trigeminal ganglion is a target in the analgesic effect of OT in the response to inflammation: the OT-induced recovery of head withdrawal threshold for mechanical stimulation, which is significantly decreased after the nerve injury, may be due to the inhibition of TRPV4 expression in the trigeminal neurons [47]. Also, these channels mediate $Ca^{2+}$ responses of retinal ganglionic cells to mechanical stimuli and inflammatory stressors [48]. However, the gating mechanism of TRPV4 differs between retinal neurons and retinal glial cells (Muller cells), where metabolites of arachidonic acid (5.6-EET) are required.

TRPV4 is involved in glial intracellular $Ca^{2+}$ transients that lead to the release of astrocyte glutamate and, as a result, enhance synaptic activity of neurons. This is hypothesized to be a constitutive mechanism of the neuro-glial regulation in response to changes in the local lipid environment [49]. TRPV4-mediated $Ca^{2+}$ inflow promotes inflammasomes activation and proinflammatory cytokines release in hippocampal astrocytes and microglia leading to the damage of CA1 and CA2 pyramidal neurons that was attenuated by TRPV4 antagonists [50].

TRPC4 channels are GPCR-operated and are involved in the signaling cascades of neurotransmitters [52] and as a counterpart of the capacitative $Ca^{2+}$ entry in endothelial and smooth muscle cells [53,54]. In neurons, these channels are shown to participate in excitotoxicity developed under glucose or oxygen deficiency where they are activated via $G_{q/11}$ coupled to metabotropic glutamate receptors [55] but there is not much data about their role in neuronal functioning. TRPCs have been demonstrated to mediate the direct OT activation of the tuberoinfundibular dopamine neurons, providing the inward current in which the low-voltage component appeared to be sensitive to 2-APB and flufenamic acid [55]. Coincident activation of $G_{q/11}$ and $G_{i/o}$ triggers TRPC4 activation in lateral septal neurons that demonstrate the above threshold plateau depolarization in response to either pharmacological coactivation of $GABA_B$Rs and mGluR1/5 receptors or electrical stimulation of fimbria–fornix fibers [56,57]. Interestingly, a similar G-protein coactivation has been established in M2/M3 muscarinic receptors activated cation currents in ileal smooth muscle cells (SMCs) [58,59]. TRPC4 together with $SK_{Ca}$ channels were shown to participate in the postsynaptic response mediated via mGluR activation giving one more evidence of the GPCR-operated properties of these channels in the CNS [60].

In visceral SMCs TRPC4 channels can contribute to the inward cation current in response to oxytocin [61] or acetylcholine [52]. Knockdown of TRPC4 gene specifically attenuates GPCR-stimulated extracellular $Ca^{2+}$-dependent increases in $[Ca^{2+}]_I$ in human myometrium cells [62]. Activation in response to hypotonic stress in isolated rat myometrium SMCs leads to the outward rectifying current that exhibits TRPC4/5-like pharmacology and appears to be mediated via GPCRs [63].

In the contractile studies using isolated myometrium strips dissected from pregnant rat uteri (18-22 day of gestation) we observed a contractile response to the selective TRPC4 agonist (-)-englerin A (1 nmol/l) that was comparable to that evoked by carbachol (50 μmol/l) or OT (10 nmol/l) (Fig. 3a). Interestingly that the blockade of TRPC4 during OT-stimulated

contractions using the highly potent antagonist Pico145 (100 pmol/l) resulted didn't change the contractile force compared to the amplitude of contractions developed in response to OT only in pregnant rats (Fig. 3b) but that blockade of TRPC4 tends to suppress the OT-induced contractions of nonpregnant rat uteri (Fig. 3c) and this effect appears to be more potent in samples taken from rats with acute kidney injury (Fig. 3d). These different effects of TRPC4 pharmacological modulation in myometrium suggest the hypothesis about the possible engagement of these channels as a fine tuning of cellular response to the neurohormonal signal but further investigation needed to complete the puzzle.

TRPC channels are also known to operate in the case of sarcoplasmic store depletion and this mechanism is described for both central neurons and smooth muscles [63–64]. In particular, TRPC3, TRPC5 role was implicated in SOCE-mediated regulation of neuronal pre- and postsynaptic activity as well as gene expression control [65] and TRPC1 demonstrated not only mGluR1-mediated but also STIM1-mediated activity in GABAergic inhibitory stratum *oriens/alveus* interneurons (O/A Ins) [66]. TRPC1/4 are shown to provide SOCE in pulmonary arterial SMCs [67], and in the myometrium [68]. On the other hand, uterine SMCs lacking functional TRPC4 channels do not demonstrate any changes in thapsigargin- or OAG-stimulated increases in $[Ca^{2+}]_i$ indicating that inhibition of $Ca^{2+}$ uptake may not involve TRPC4 in the process of $Ca^{2+}$ store refilling [62].

## DISCUSSION

TRP ion channels in the myometrium participate in the regulation of cellular excitability and contractility and their pharmacological

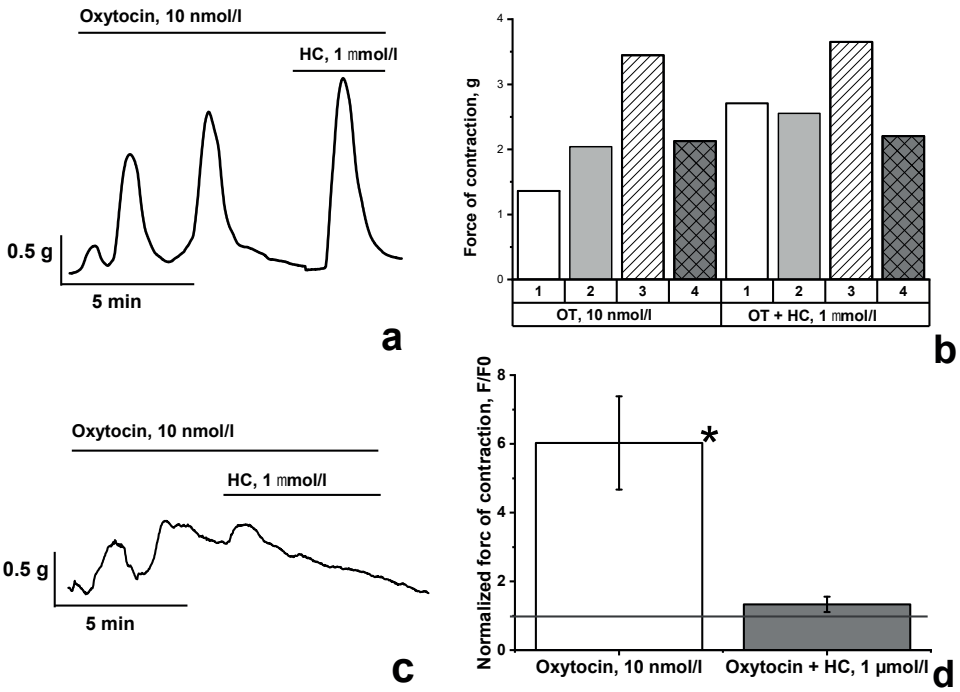


Fig. 2. TRPV4 contribute to the OT regulation of myometrium contractility. Typical trace (a) of the contractile force of isolated myometrium strip of human myometrium (methodology modified according to [46], experiments approved by the Institutional Ethics Committee for Research Protocol #4 dated 10 October 2018) and changes of tension level (b) during OT application followed by TRPV4 inhibition demonstrate the increase of contractility in one group of samples. Another group of strips (c, d) demonstrated the decrease of the tension level; M±m, n=4, *P<0.05 relative to the control marked as a straight line. OT – oxytocin, HC - specific antagonist HC067047 of TRPV4.

modulation alters the tissue response to OT. Colocalization of TRPV4 together with $BK_{Ca}$ channels in caveolae (lipid raft membrane microdomains typical to myocytes) [42] may be considered as a limitation factor for both duration and strength of OT-induced contractions (Fig. 4).

Thus, TRPV4 represents a $Ca^{2+}$ permeable multimodal channel that is involved in the effector pathways [70,71] when examined in visceral tissues can provide specific insights about the interaction and cross-regulation between the mechanisms that underlie TRPV4-mediated cellular excitability in sensory neurons [72].

In visceral smooth muscles as well as neurons TRPC4 is shown to be engaged either as a GPCR-operated or SOC channel [53,57]. TRPC4 participates in the oxytocin-stimulated activity of the myometrium being a source for maintaining contractions [62,69]. Thus, OT-triggered TRPC4 is likely to participate in the regulation of membrane excitability and other aspects of neuronal physiology (Fig. 4).

Neurons within the CNS and visceral SMC demonstrate the similar pool of ion channels that are involved in OT signaling or may be affected by it: various TRP channels, $BK_{Ca}$ channels, $Ca^{2+}$-dependent $Cl^-$ channels [54,72,73] and are affected by the same modulators as in neurons. TRPV4 and TRPC4 are those channels being expressed both in the CNS and visceral SMCs and they are involved in the same processes (table) but their exact role on OT effect remains unclear. Thus, the results obtained on SMC may contribute to the puzzle of complex OT signaling in neurons.

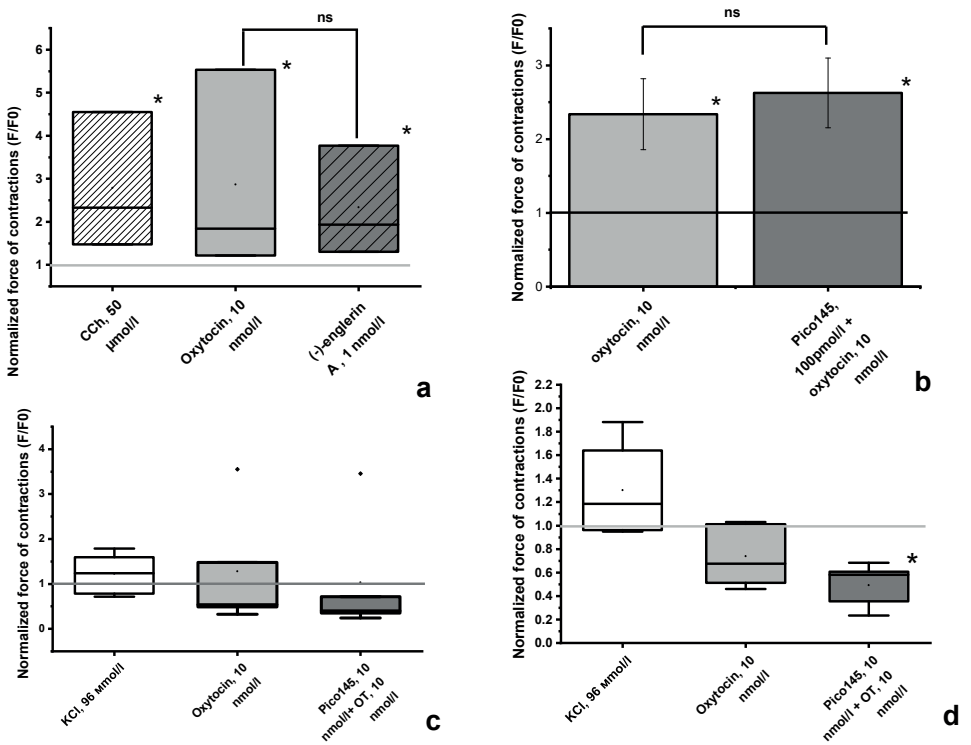


Figure 3. TRPC4 participates in OT-stimulated contractions in rat myometrium under its different physiological states. Selective TRPC4 agonist (-)-englerine A demonstrates uterotonic effect (a) in the late pregnant myometrium (Me, Q1-Q3, n=9, *P<0.05 compared to control marked as a straight line). The contractile force remained unchanged under TRPC4 antagonist (b) in the late pregnant myometrium tissue (; M±m, n=4) but in nonpregnant rat uterus, TRPC4 contributed to the stimulatory effect of OT (c; Me, Q1-Q3; n=5; *P<0.05 compared to control). In the case of acute kidney injury induced by glycerol administration (3 injections of 50% water solution in the dose of 10 ml/kg) the decrease of contractile force at TRPC4 inhibition becomes more pronounced (d; Me, Q1-Q3; n=5; *P<0.05 relative to control); CCh – carbachol, OT – oxytocin, methods used – ex vivo isometric force recording (a,b) and ex vivo intrauterine pressure registration (c,d).

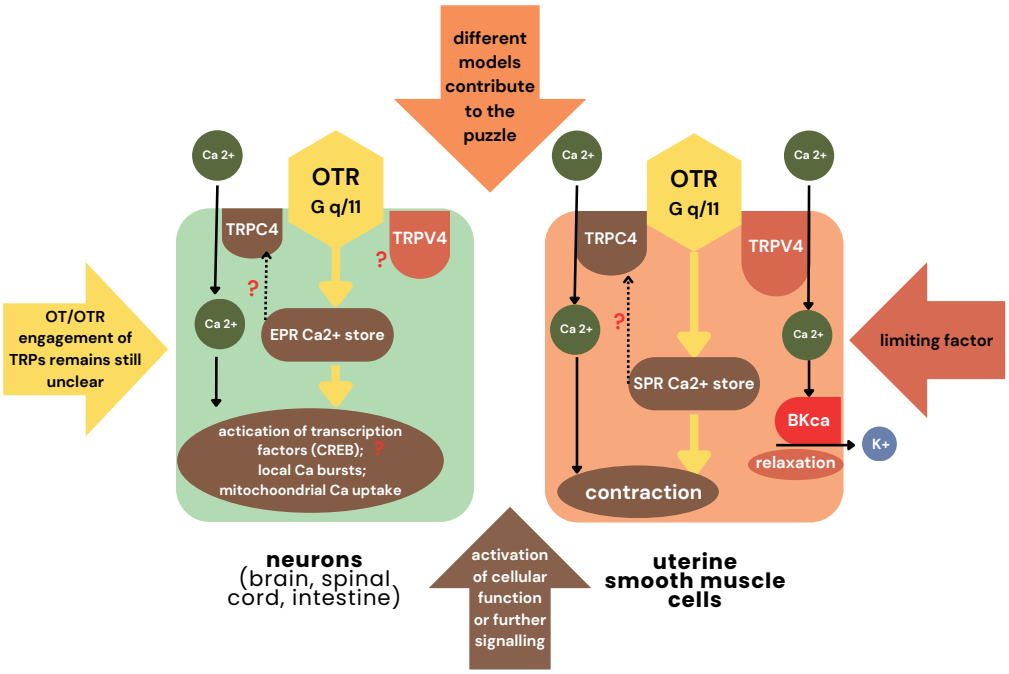


Figure 4. TRP ion channels participate in OT-induced effects in human and rat myometrium and neurons

Thus, there is a perspective to treat the data obtained in neurons and SMCs as complementary in the investigation of intracellular pathways and their impact on cell excitability. It is possible that TRP channels in OT neurons can contribute to the regulation of their spiking properties (frequency, transient vs. steady-state activity, firing patterns), similarly to the thermosensitive TRPs in *Drosophila* sensory neurons [76]. Finally, SMCs may be a more convenient but relevant model that can help to clarify the mechanisms of OT-$Ca^{2+}$ signaling involved in the regulation of neuronal excitability, neurotransmitter release, synaptic transmission and plasticity.

*Conflict of Interest*

*The authors of this study confirm that the research and publication of the results were not associated*

**TRPV4 and TRPC4 are expressed and engaged in neuronal, glial and smooth muscle functioning**

| Ion channels | Type of cells | | |
|---|---|---|---|
| | neurons | glia | smooth muscle cells |
| | **Expression in cell types** | | |
| TRPV4 | + | + | + |
| TRPC4 | + | -/+ | + |
| | **Effect when activated/blocked** | | |
| TRPV4 | neuronal excitability, synaptic activity [47] | $Ca^{2+}$ concentration changes [50] | local $Ca^{2+}$ transients and activity of $Ca^{2+}$-activated ion channels [41–43] |
| TRPC4 | membrane depolarization [58] | $[Ca^{2+}]_i$ regulation in fetal astrocytes [74] | ROCE and SOCE [61,62,68,69] |

*with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.*

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## ФУНКЦІОНУВАННЯ ОКСИТОЦИНОВИХ РЕЦЕПТОРІВ У ЦЕНТРАЛЬНІЙ НЕРВОВІЙ СИСТЕМІ ТА ГЛАДЕНЬКИХ М'ЯЗАХ

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Вивчення механізмів нейронних зв'язків лежить в основі фундаментальних відкриттів, спрямованих на підтримку здоров'я. Дослідження передачі сигналів від окситоцину в нейронах або всередині різних ділянок мозку спрямовані на з'ясування ролі цього нейрогормонального модулятора в регуляції синаптичної передачі, пластичності та збудливості нейронів, які залучені у репродуктивній функції, соціальній поведінці, здатності до навчання, тривозі, а також поширення запалення та диференціювання в головному мозку. Окситоцин синтезується в супраоптичних і паравентрикулярних ядрах гіпоталамуса і при виділенні в кров із задньої частки гіпофіза впливає на скорочення матки і лактацію. У той же час цей нонапептид, діючи в лімбічній системі та корі головного мозку, модулює активність нейронів, змінюючи стан іонних каналів на їх мембранах. Окситоциновий рецептор здебільшого пов›язаний з Gq/11 білками, що призводить до активації фосфоліпази С і вивільнення $Ca^{2+}$. Ці шляхи є центральними для регуляції активності різних типів каналів тимчасового рецепторного потенціалу (TRP), особливо канонічної підродини каналів TRPC. В огляді ми підкреслюємо зв'язок між внутрішньоклітинного сигналізацією окситоцину, яка особливо добре досліджена в міометрії, і рецепторомкерованими TRPC4 і мультимодальними TRPV4 іонними каналами, що беруть участь в регуляції скоротливості гладкої мускулатури матки за різних умов. Важливо, що, як і окситоцин, ці канали виявились залученими до механізмів невропатичного болю, тривоги, страху та депресії. Оскільки подібні до гладеньком›язових шляхи передачі сигналу, ймовірно, будуть дієвими і в нервових клітинах, ми пропонуємо, щоб майбутні дослідження ефектів окситоцину в ЦНС також брали до уваги роль цих $Ca^{2+}$-проникних каналів.

Ключові слова: окситоцин, нейрони, головний мозок, гладенькі м›язи, іонні канали

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