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Fast kinetics of fundamental aortic contraction to phenylephrine compared to KCl only in male prepubertal and adult rats

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Abstract

Background: *Phenylephrine (PHE) produces higher aortothoracic contractile tension with endothelium (T[ON]) compared to potassium chloride (KCl). Both are exponential triphasic responses (Φ1, Φ2, Φ3) but their kinetics have not been compared with the time constant (τ in s). Goal. To study the triphasic T[On] kinetics (τ: Φ1, Φ2(fundamental) and Φ3) of 1μM PHE vs 40mM KCl.* **Material and methods:** *We compared numerical values of τ1, τ2, τ3 of the T[On] of prepubertal male Wistar rats (without established reproductive capacity) with adult male ones.* **Results:** *Φ2 showed higher gain (g), shorter delay time (s), and faster kinetics of T[On] at PHE than at KCl.* **Conclusions:** *In the time course of T[On] only the fundamental exponential phase was faster with PHE than with KCl.*

Keywords: *Aorta. Tension. Kinetic. Exponential. Phenylephrine. KCl.*

Introduction

The tension generation resides in the contractile proteins of the vascular smooth muscle cell[1]. A G protein-coupled receptor (GPCR) agonist, such as phenylephrine (PHE)[2], produces greater tension by increasing the concentration of intracellular calcium ($[Ca^{2+}]i$) compared to KCl[3] probably based on its different mechanism of action; KCl is a convenient stimulus to evade GPCRs and activate smooth muscle through a highly reproducible mechanism that involves activating the Ca^{2+} channels operated by voltage leading to increases in Ca^{2+} cytosolic free, which activates the Ca-dependent myosin light chain (MLC) kinase^{2+}-calmodulin, phosphorylation and contraction of the vascular smooth muscle cell (MLCV) as well as a calcium-sensitizing stimulus[4,5]. This KCl-induced stimulus-response mechanism is used in comparative studies to explore more complex mechanisms generated by GPCR activation[5,6]; as is the case with PHE, which activates the α-adrenergic receptor$_{1D}$ coupled to heterotrimeric G protein (Gq11 and G12/139) activates phospholipase C (PLC) to promote the hydrolysis of phosphatidylinositol bisphosphate to

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diacylglycerol (DAG) and inositol triphosphate (IP3), IP3 can serve as an agonist for the release of Here^{2+} of intracellular reserves to increase [Ca^{2+}] intracellular and cause contraction in the rat aorta. There is also sensitisation of the contractile elements at Ca^{2+} in the rat aorta mediated by a cyclic guanosine monophosphate (GTP) binding protein coupled with the α adrenergic receptor (AR) such as phenylephrine (PHE, pharmacological agonist of RAα) and norepinephrine (NE, endogenous agonist of RAα)[6] cause smooth muscle contraction[6].

Current status

The kinetics (rate of exchange per s) of transient aortothoracic contractile with functional endothelium (T[On]) induced by PHE or KCl is triphasic exponential in each case[7,8]. Purpose, compare the kinetics of T[On]) to PHE and KCl in male rats 4.5, 6.1 and 16.4 weeks, resulting from its adjustment with a 3-component model (time delay) included in its 10 parameters (M3C, 10P) previously evaluated[7,8]. We used prepubertal male rats of 4.5 and 6.1 weeks without established reproductive capacity, with the goal to look for kinetic differences of T[On] with respect to adult male rats (16.4 weeks) already with reproductive capacity. The importance of comparing the kinetics of T[On]) between prepubertal male rats and adult female rats was that we did not know whether the endocrine (eg, androgenic) background, which we assume is already well established in adult female rats, could have some effect on the rate of exchange of T[On]PHE and KCl that results in different numerical values of τ between prepubertal and adult rats[9].

Hypotheses

If the numerical duration of the time constant τ en s (kinetics) from T[On] to PHE or KCl is different, then the three exponential phases adjusted with the M3C,10P (T[On]: τ Φ1, τ Φ2, τ Φ3) should be faster for the condition (PHE vs KCl) x group (τ: PHE < KCl).

Material and methods

Chemicals

PHE, KCl and acetylcholine (Acth) were purchased from Sigma. Sodium pentobarbital is obtained from Pfizer. Type I ultrapure water is used.

Animals. Ethical approval

Three groups of male Wistar rats (3G) of different ages and weeks were formed[9] en g (mean±SD) of n = 6 per group[10]: 4.5 weeks (JPrep, prepubertal youth); 6.1 weeks (Prep); y of 16.4 weeks (Adu); approved by the Animal Care Committee of the Laboratory of our Institution (30233/04-20220216/20230675)[10]. With the JPre and Pre we wished to count on the nearby windows before the reproductive capacity with respect to the adults.

Sample preparation and vascular reactivity

Anesthetised animals were bleded[11]. The thoracic aorta with functional endothelium was placed in cold oxygenated Krebs-Ringer bicarbonate (SRK) solution to obtain 3 or 4 rings of 4 to 5 mm in length, which were mounted in 10 ml baths for their bioassay with PHE 1μM[7,12] or KCl 40mM[8] (Condition: PHE or KCl). The value of the transient tension of the isometric contraction of T[On] from the beginning of the condition (Onset) to the asymptotic state, the required value (Offset) was measured with a model 1030 force release transducer (UFI) and recorded online with AcqKnowledge software (MP100WSW; Biopac Sistemas, Inc., Santa Barbara, California, USA)[7,12].

Previous precontractile reference line (T[Basal]), PHE 1μM was added in the bioassay to obtain the T[On] Condition. The endothelium was verified by the presence of at least 80% of relaxation in response to ACTH 1μM after preconstrict the tissues with PHE 1μM[12].

Modelling

M3C,10P[7] adjusted the transitory time course of T[On]Condition, in a window from T[basal]) until the end of T[On]Condition in g (M3C,10P{T[basal]_T[On]Condition}), with consecutive exponential transient time periods through 10P previously described[7], to obtain the three-phase adjustment T[On] (T[On]Modelled in g: T[On]Φ1, T[On]Φ2, T[On]Φ3; Φ, phase) and its kinetics (τ, time constant in s): τ Φ1, τ Φ2, τ Φ3).

Data collection and analysis

To improve the signal-to-noise ratio, the T[On]Condition of 3 to 4 rings per rat (single average response) were aligned and overlapped, for their adjustment with the M3C,10P (T[On]Modeled)[7] through computed linear regression[13] of the 3G. The 10P of three expected kinetic phases were evaluated (e.g., τ: Φ1, Φ2, Φ3) based

on three preceding physiological events (S1, S2, S3)[14,7]. The goodness of the adjustment of the experimental data by the M3C,10P{T[basal]_T[On]Condition} was evaluated using the lowest residuals of the sum of squares (RSS values) or the minimum squared error (MSE values) of each adjustment made[13].

Statistical analysis

Data of interest were analysed using analysis of variance (ANOVA) of two factors (condition x group) and the F values were only presented where p <0.05. The *post hoc* Holm-Sidak (F) was carried out to compare kinetic parameters, when appropriate[15].

Results

The time course of M3C,10P{T[basal] _T[On]Condition}, of each rat per group and its corresponding adjustment curves are shown in it Figure 1A and B respectively, with an example of modelled the *three-phase exponential adjustment* (Fig. 1C-D respectively). The analysis of T[On]experimental showed; in the condition (PHE 1µM, 40mM KCl) df (degrees of freedom) = 1, F = 4.953 y p = 0.034; in the group (4.5, 6.1 and 16.4 weeks of age) df = 2, F = 16.339 and p < 0.001; and in the interaction (condition x group) df = 2, F = 3.619, p = 0.039. The analysis of T[On]model showed; in the condition (PHE 1µM, 40mM KCl) df = 1, F = 4.1218 y p = 0.0513; in the group (4.5, 6.1 and 16.4 weeks of age) df = 2, F = 17.1167 and p < 0.001; y in the interaction (condition x df group = 2, F = 1.7632, p = 0.1888. The analysis of T[On]a2 showed; in the condition df = 1, F = 17,529; in the df group = 2, F = 30,886; and in the interaction df = 2, F = 5.088. The analysis of T[On]td2 showed; in the condition df = 1, F = 427.128; in the gl group = 2, F = 37,161; and in the interaction df = 2, F = 25,639. The analysis of T[On]tau2 showed; in the condition df = 1, F = 90,459; in the gl group = 2, F = 7.348; and in the interaction df = 2, F = 13.216.

T[On]: experimental vs modelled.- The global analysis of T[On]experimental multiple comparison and post hoc (Holm-Sidak method) resulted (mean ± SEM); significant between groups (different superindex letter pairs: ^{a}16.4 (2.8722 ± 0.1079) > {^{b}4.5 (2.2882 ± 0.0578) p < 0.001, ^{b}6.1 (2.3393 ± 0.039) p < 0.001) en PHE 1µM, but not (p > 0.05) in KCl 40mm (16.4 (2.4945 ± 0.1215) p = 0.189, 4.5 (2.288 ± 0.0434) p = 0.155, 6.1 (2.29767 ± 0.0487) p = 0.93) and On]experimental group 16.4 was significantly higher (p < 0.002) on PHE 1µM compared to KCL 40mM. The global analysis of T[On]modelled of multiple comparison and *post hoc* resulted; not significant (p > 0.05) between groups: 16.4 (2.9196 ± 0.1096), 4.5 (2.35002 ± 0.0630), 6.1 (2.3703 ± 0.0413) en PHE 1µM, but significant (p < 0.001) in 40mM KCl (^{a}16.4 (2.5999 ± 0.1407) > {^{b}4.5 (2.3115 ± 0.0447), ^{b}6.1 (2.3126 ± 0.0499), p = 0.899} and the interaction showed that T[On]modelled {PHE 1µM similar to KCL 40mM} from the 16.4 group, were significantly higher (p < 0.005 and p < 0.008 respectively) compared to the rest of the groups (4.5, 6.1). In general, a similar trend was observed in the experimental and modelled T[On]which is why the global average of experimental T[On] (2.43 ± 0.0459) was not objectively different (n = 36, p > 0.05) compared to T[On]modeled (2.477 ± 0.0489), which validated the consistency of the M3C,10P when adjusting the experimental data.

There *Φ2 (a, td, tau):* PHE 1µM *vs* KCl 40mM.- The overall analysis of T[On]a_2 of multiple comparison and *post hoc* resulted (Fig. 1E) significant (pairs of different letters in superscript); between conditions, PHE 1µM > KCL 40mM ^{b} (p < 0.001), between groups: 16.4^{a}, 4.5^{b}, 6.1^{b} (p < 0.001) and the interaction showed that 1µM 16.4^{a}, KCl x 40mM 16.4^{b}, PHE 1µM x 6.1^{b}, PHE 1µM x 4.5^{b}, KCl 40mM x 6.1^{b}, KCl 40mM x 4.5^{b} (p = 0.013). The global analysis of T[On]td2 of multiple comparison and *post hoc* resulted (Fig. 1F) significant; between conditions; KCl 40mM ^{a} > PHE 1µM^{b} (p < 0.001), between groups: 16.4^{b}, 4.5^{b}, 6.1^{a} (p < 0.001) and in the interaction (condition x group) showed that KCl 40Mm 6.1^{a}, KCl 40mM 16.4^{b}, KCl 40mM 4.5^{b}, PHE 1µM 4.5^{c}, PHE 1µM 6.1^{c}, PHE 1µM 16.4^{d} (p < 0.001). The global analysis of T[On]tau2 of multiple comparison and *post hoc* resulted (Fig. 1G) significant; between conditions; KCL 40mM ^{a} > PHE 1µM^{b} (p <0.001), between groups: 16.4^{b}, 4.5^{b}, 6.1^{a} (p = 0.003) and in the interaction it showed that KCl 40mM 6.1^{a}, KCl 40mM 16.4^{b}, KCl 40mM 4.5^{b}, PHE 1µM 16.4^{b,c}, PHE 1µM 6.1^{c,d}, PHE 1µM 4.5^{d} (p < 0.001).

Discussion

We studied whether the kinetics (τ) of T[On] was faster for PHE than for KCl; so, in T[On] a KCl it is known that there is depolarization of the membrane, entry of Ca^{2+} through the channels of Ca^{2+} voltage operated (VOCC)[6], activation of the myosin light chain kinase (MLCK) dependent on Ca^{2+} and increase MLC phosphorylation; whereas T[On] a PHE, mediated by GPCR, causes activation of heterotrimeric proteins Gq11 and G12/139, which leads

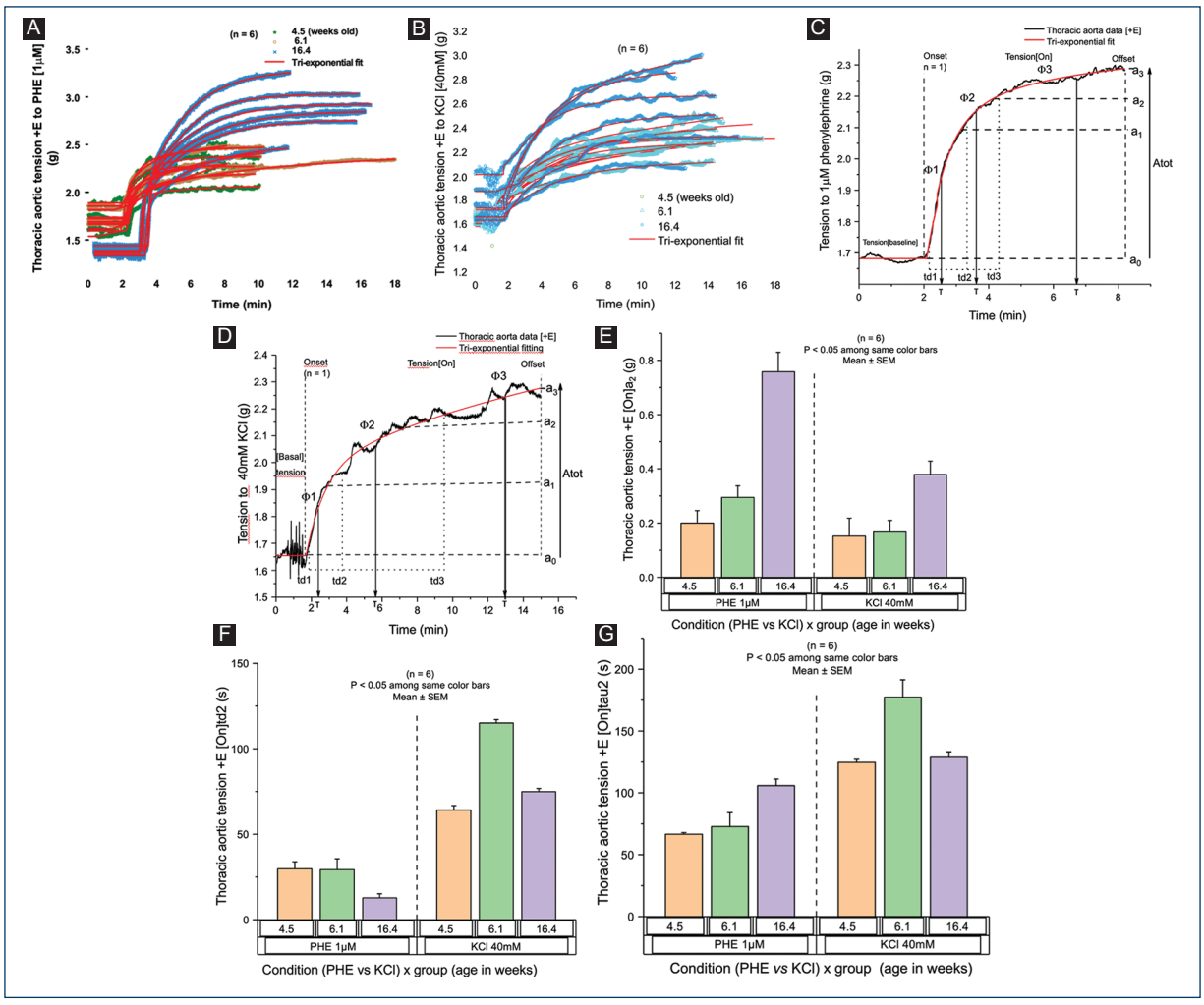

Figure 1. Time course of aortothoracic tension with functional endothelium (+E) in prepubertal (4.5 and 6.1 weeks of age) and adult (16.4 weeks of age) male rats. Transient contractile tension (Tension [On]). **A:** induced with 1μM phenylephrine. **B:** with KCl40mM). Fitted with the three-component exponential mathematical model (delay times) with 10 parameters (M3C,10P: tri-exponential fit of experimental data). **C** and **D:** with an individual example of that adjustment respectively. (n), sample size. g, grams. Adjustment window, basal line_Start up to the end of the total answer and identify three phases (Φ1, Φ2 and Φ3) with their respective kinetics: fast (τ Φ1), moderately fast (τ Φ2), and slow (τ Φ3). Numbers 1, 2 and 3, phase number.10P: a_0, a_1, a_2, a_3 (a, amplitude of answer in g, $A_{total} = (a_1 + a_2 + a_3)$; td1, td2, td3 (td, delay time or component in min); τ1, τ2, τ3 (τ, time constant in min). Comparison of the amplitude parameters. **E:** a_2. **F:** td2 en s. **G:** τ en s of the fundamental phase (Φ2). (n = 6), sample size. Media, average height of the bar. EEM, standard error of the mean (vertical line over the bar). Objective difference ($p < 0.05$) between the mean values of the two pharmacological conditions (pair of bars of the same color).

to the generation of multiple cellular messengers, including inositol 1,4,5-triphosphate (IP3), diacylglycerol (DAG) and low molecular weight GTPasa, RhoA[10], with activation of multiple types of Ca channels^{2+} and activation of at least two kinases, the RhoA kinase (ROK) and the protein kinase C (PKC), in addition to the Ca-dependent MLCK11^{2+}, which leads one to think that the majority of non-genomic signals generated after GPCR stimulation are regulated in the plasma membrane[5]. Here we find that T[On] a KCl reaches its final maximum a few minutes later than PHE; but both T[On] had similar maximum tensions and maybe also an equivalence in stimulation intensity with PHE and KCl, but T[On] had different kinetics that we attribute to the different causal mechanisms of PHE and KCl in the dynamics of increment of la [Ca2+]i[6.5] in the development of the T[On][1]. Thus, we observed for the first time, a faster T[On]Φ2 kinetics with PHE than with KCl (PHE[τ2 < KCl[τ2).

High [K^+] extracellular (e), as in this work (40mM), it is known that it depolarizes the cell membrane, opens VOCCs, increases the influx of Ca^{2+} and causes sustained contraction[14,16] which was observed in this work as well (Fig. 1B) and it is also known that staggered changes in the membrane potential (Vm) modulate contraction via Vm and phospholipase C, releasing DAG and IP3[17] and it would explain in part a three-phase exponential T[On] at KCl 40mM observed here. However, the strength quotient/[Ca^{2+}]i in general is greater during pharmacomechanical activation than during contractions activated by depolarization[17]. On the other hand, noradrenaline (NA) causes the release of Ca^{2+} of RS and initiates vascular smooth muscle cell contraction14 and changes in [Ca^{2+}]i influence the vascular function and the regulation of blood pressure, involving specific fluctuations in[Ca^{2+}]i[16]. But the amount of Ca^{2+} stored in the sarcoplasmic reticulum (Ca^{2+} of RS) is limited, so T[On] is transitory; likewise, such as Ca^{2+} channel blockers do not inhibit the release of Ca^{2+} from the RS and the NA also opens the channel of Ca^{2+} linked to the receptor, it increases the influx of Ca^{2+} and causes T[On] sustained at PHE 1μM, also observed here (Fig. 1A). Thus, the largest influence of Ca^{2+} in the arthoracic smooth muscle tissue with endothelium induced by PHE, would explain here for the first time the greater gain of the bioassay system with faster delay times and T[On] kinetics compared to those induced by KCl.

Φ2 (a, td, tau): comparison between groups by age of rats

In this work it was observed that the greatest T[On] a_2 from the group of 16.4 compared with those of {4.5, 6.1} weeks of chronological age, which would explain why the smooth muscle layer of the thoracic aorta of the adult rat (16.4) in contrast to the prepubertal ones, we assume that its growth has completed, responsible directly for the tension of the vascular wall and which is the white tissue of a large amount of vasoactive substances[7-9,18].

A general tendency of slow T[On]td2 to KCl compared to that of PHE in 3G, would be attributed to the fact that the stimulus with KCl causes contraction of lesser intensity compared to PHE[2,3]; which was reflected, in a slower heterogeneous T[On]td2 in 6.1 compared to {16.4, 4.5} as well as in a heterogeneity in td2 of 3G observed in the interaction in this studio (KCl 40Mm 6.1> {KCl 40mM 16.4, KCl 40mM 4.5} > {PHE 1μM 4.5, PHE 1μM 6.1,} > PHE 1μM 16.4, could possibly be explained by a complex series of interactions of growth and development[7,8,19] which we assume to occur among these groups of prepubertal and adult rats[9]. Similarly[7,8], the T[On]tau2 of the groups was of slow kinetics (tau2 of greater numerical value, >) in {6.1,16.4} > 4.5, and for this reason it was also so in the interaction {KCl 40mM 6.1} > {KCl 40mM 16.4, KCl 40mM 4.5, PHE 1μM 16.4} > PHE 1μM 16.4 similar PHE 1μM 6.1} > PHE 1μM 6.1 > de PHE 1μM 4.5; this kinetic heterogeneity between the 3G groups could also be explained, in part, by spontaneous fluctuations in vasomotor tone and diameter, modulated by regulatory systems, such as the renin-angiotensin-aldosterone system[20], baroreceptor reflexes[21], chemoreceptors[22], afferent neuronal pathways, control centres in the spinal bulb[23], parasympathetic and sympathetic efferent neuronal pathways[24], as well as local vasomotor substances[25] and endothelial; that we assume, can go on remodeling the arterial vessels in the organisms in development in the prepuberal female rats towards adulthood, designed to help regulate the arterial pressure[26].

Soon, *the fundamental phase (Φ2) of the T[On] showed greater gain and faster kinetics in the condition: τ Φ2 with PHE < KCl x group (τ Φ2 in the 3G with PHE < KCl).*

Conclusions

The time course of T[On] showed only in its exponential (fundamental) phase greater gain, delay time and faster kinetics with PHE than with KCl.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that no experiments on humans or animals have been performed for this research.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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