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Editorial Open Access

The Control of Vascular Smooth Muscle Tone: Concepts Coming from Ca^{2+} and cAMP Signalling

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Editorial

The vascular smooth muscle tone must be well-controlled to assure a perfect regulation of blood pressure. In this arena, we have two important intracellular messengers: Ca^{2+} and cAMP. Classically, the rise of intracellular Ca^{2+} within vascular smooth muscle cells starts a well-organized symphony which reaches into muscle contraction. Nowadays, we know that Ca^{2+} is an essential messenger that regulates vascular smooth muscle tone. Thus, a dysregulation of Ca^{2+} signalling may cause interferences on vascular tone.

Besides Ca^{2+}, there is another important messenger who regulates vascular tone: cAMP. But here, exerting an opposite effect compared to Ca^{2+}: rising cAMP inside vascular smooth muscle cells relaxes smooth muscle, instead of contracting them like Ca^{2+} does! Evidences indicate that cAMP may interfere on intracellular Ca^{2+} stores like endoplasmic reticulum or may exert a direct effect on the contractile machinery, thus interfering with muscle contraction. Well, we have two messengers exerting opposite effects: One contracts, and the other one relaxes vascular smooth muscle. Thus, it is not surprising that some drugs act by interfering with these messengers, e.g.: α1 adrenoceptors antagonists as prazosin, which reduces the activity of α1 adrenoceptors, thus reducing the activity of Ca^{2+} signalling, then reducing the vascular smooth muscle tone, so used as antihypertensive medications. In addition, phosphodiesterase inhibitors, which reduce the degradation of cAMP, thus enhancing the activity of cAMP signalling, are also used to relax the smooth muscle. Well, what would happen if we combine drugs which reduce Ca^{2+} signalling activity as Ca^{2+} channel blockers, and drugs which enhance cAMP signalling activity as phosphodiesterase inhibitors? Obviously, you may say: If these drugs alone relax smooth muscle, when we combine them, we should have a drastic relaxation of the smooth muscle! Are you sure? If the cells worked in a mathematic and linear way, you would be right! But, it is not like that!

In 2013, we discovered that the combination of these drugs, Ca^{2+} channel blockers and phosphodiesterase inhibitors, causes a drastic contraction of the smooth muscle, instead of relaxing it, an apparent puzzling result! Yeah, almost all great discoveries come from puzzling results [1]! But, how to explain this? The answer: The vascular smooth muscle tone is also regulated by sympathetic nerves, which release neurotransmitters that achieve vascular smooth muscles, e.g.: ATP and noradrenaline [2,3]. These neurotransmitters induce the contraction of the vascular smooth muscle. Here is the thing: as in the vascular smooth muscle cell, in the sympathetic neuron, the rise of Ca^{2+} also activates its function. In the case of sympathetic neurons, it releases the neurotransmitters. However, while rising cAMP relaxes the smooth muscle, its rising inside neurons also increases the release of neurotransmitter, such as elevating Ca^{2+} does! So, when we combined those drugs, Ca^{2+} channel blockers and phosphodiesterase inhibitors, they will indeed relax smooth muscle, however, in the neurons, they will exacerbate the release of neurotransmitters [4]! This massive release of neurotransmitters will oppose the relaxation effect, and will predominate against it, thus we have the smooth muscle contraction! Again, you may see: ok, but why is this happening in neurons? If we are reducing Ca^{2+} signalling activity in neurons through Ca^{2+} channel blockers, shouldn´t they reduce the neurotransmitter release? Because here we have the Ca^{2+}/cAMP signalling interaction, which we discovered [1]! By reducing Ca^{2+} signalling activity in neurons, this issue increases the activity of cAMP signalling. Thus, the combination of Ca^{2+} channel blockers with the drug (phosphodiesterase inhibitor) which enhances the cAMP signalling activity will thus enhance, much more, this effect! Thus, the rising of cAMP levels within neurons will thus increase the release of neurotransmitter as net effect, achieving vascular smooth muscle, which then contracts! Isn´t it very interesting? In addition, sometime later, another interesting study appeared describing the existence of similar Ca^{2+}/cAMP signalling interaction in skeletal muscle [5]. But this is an issue for another article.

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