Analysis on mechanisms of glucose uptake on high K^+-induced contraction in smooth muscle

Summary of Doctoral Thesis

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Summary

Glucose is one of the most important energy substrate in organism. Glucose uptake into a cell is mainly achieved by sodium-glucose cotransporter (SGLT) and glucose transporter (GLUT).

Smooth muscles are classified into phasic and tonic muscle by characters of electrophysiological and mechanical reaction. It has been suggested that differences between phasic and tonic muscle are also related to the dependence of the aerobic metabolism. Moreover, it may be suggested that the relationship between contractile response and mechanisms of glucose uptake in muscles differ from each tissues.

On the other hand, phloridzin, an inhibitor of SGLT, inhibits high K^+-induced contraction, but the inhibitory effect differ from each types. It has been suggested that the relaxing mechanism is inhibition of glucose uptake via SGLT. However, there is no report shows that the effect of phloridzin on glucose uptake in smooth muscles. It has been reported that aorta, a tonic muscle, expressed GLUT4 and glucose uptake was mediated by insulin and receptor agonist. Activation signals of GLUT4 differ from each organ. However, there are few reports show which the GLUT4 signaling on the differences between normal and hypoxic condition in aorta.

Thus, the present study examined that the relationship between inhibition of high K^+-induced contraction and glucose uptake in phasic muscle, and activation signals on insulin and high K+-induced contraction, inhibition of aerobic metabolism in tonic muscle to provide the new findings contribute to make the function of visceral organ in pathophysiological condition such as shock, starved state or diabetes.

The relationship between high K^+-induced muscle contraction and glucose uptake in phasic muscle.

In present study, inhibition of aerobic metabolism inhibited high K^+-induced muscle contraction in smooth muscle. The inhibition of muscle contraction was remarkably in phasic muscle such as iris sphincter and ileum, but slightly that in tonic muscle such as aorta. Similarly, phloridzin, SGLT inhibitor, remarkably inhibited high K^+-induced muscle contraction in iris sphincter and ileum, but slightly inhibited that in aorta. SGLT1 mRNA was highly expressed in ileum, but SGLT2 mRNA expression was low. On the other hand, the SGLT 1 and 2 mRNA were lowly expressed in aorta. Moreover, application of high K^+ increased glucose uptake in ileum. Furthermore, additional application of phloridzin inhibited high K^+-induced glucose uptake. These results

suggest that the high K^+-induced contraction in ileum highly depends on aerobic metabolism and relates to glucose uptake via SGLT1 to maintain the muscle contraction.

The relationship between high K^+-induced muscle contraction and glucose uptake in tonic muscle.

GLUT4 is expressed in skeletal muscle and adipocyte, but it does in aorta, too. The present study showed expression of GLUT4 mRNA in rat aorta. Furthermore, application of insulin increased glucose uptake and GLUT4 translocation to membrane in aorta. The increase was inhibited by application of PI3K and Akt inhibitor, but not by AMPK inhibitor. Theses results suggest that the GLUT4 is activated via PI3K/Akt pathway in aorta, similar to skeletal muscle. However, the application of high K^+ did not affect glucose uptake in aorta. This result suggests that aortic smooth muscle contraction highly depends on exogenous energy substrate such as glycogen, but not endogenous energy substrate differ from skeletal muscle. Simultaneous application of high K^+ and NaCN increased glucose uptake and GLUT4 translocation to plasma membrane. The increase of glucose uptake was inhibited by application of AMPK

inhibitor, but not PI3K/Akt inhibitor. However, the increase of GLUT4 translocation was inhibited PI3K/Akt and AMPK inhibitor. These results suggest that that the inhibition of aerobic metabolism on muscle contraction activates several glucose transporters which depend on AMPK activation. It remains unclear what kinds of glucose transporter relating to muscle contraction. According to the above reasons, in rat aorta, insulin dependent and independent glucose uptake and signaling are similar to those of skeletal muscle. On the other hand, it may be suggested that the high K^+-induced muscle contraction depends on endogenous energy substrate, but the inhibition of aerobic metabolism activates several glucose transporters in aorta. Specifically, it may be implied that GLUT4 translocation needs stimulation of AMPK in aorta. This study demonstrated GLUT4-related signals and mechanisms of glucose uptake on high K^+-induced muscle contraction and inhibition of aerobic metabolism in aorta at the first time.

Conclusion

According to the above results, it was suggested that high K^+-induced contraction highly depends on aerobic metabolism and increases glucose uptake via SGLT1 in iris sphincter and ileum as phasic muscle.

On the other hand, aorta was expressed insulin dependent glucose uptake and signaling via GLUT4, as well as skeletal muscle and adipocyte. However, it was different from skeletal muscle that high K^+-induced contraction do not stimulate GLUT4 in aorta. Moreover, NaCN-induced decreases of aerobic metabolism, slightly inhibited high K^+-induced contraction and increased glucose uptake via GLUT4 as well as skeletal muscle. Furthermore, the mechanisms of glucose uptake of smooth muscle differ from organs at the first time. These knowledges probably provide the data contribute to make clear the function of visceral organ in pathophysiological condition such as shock or starved state.