Application of Principles of Systems Biology to investigate facilitation of action of a multi-component medication, Shakuyaku-kanzo-to (SKT), by interstitial potassium

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INTRODUCTION

SKT (a 1:1 combination of root extracts from Paeony and Licorice) is used in the treatment of muscle cramp. We used the principles of Multi-Scale Systems Biology (Noble, 2008), including "no privileged level of causation", to drill down from organ, tissue and cell levels towards molecular processes controlling smooth and skeletal muscle contraction (Tasaki et al, 2015).

HYPOTHESIS

A systems analysis of contracting muscle showing many ionic and metabolic changes led to our hypothesis that the pathological state of muscle spasm or cramp might be enabling a much lower dose of SKT to act.

RESULTS

Our results show that by mimicking part of such a state by doubling extracellular potassium, SKT relaxes contracting skeletal muscle at a much lower dose (Sam et al, 2015 a,b). Increased interstitial potassium therefore facilitates the relaxing action.

FIGURE LEGENDS

Figure 1. SKT at 1 mg/ml has small or no action on twitch tension of diaphragm muscle of guinea-pig in normal physiological solution (5.4 [K^+]), whereas 10 mg/ml abolishes twitch within about 30 minutes (Sam et al 2015a).
Figure 2. Dose response curve 5.4 [K+] is steep, with an IC50 around 5 mg/ml.
Figure 3. SKT at 1 mg/ml completely abolished twitch contraction in 10.8 mM external potassium.
Figure 4. Results of several experiments (n=9) at 1 mg/ml to show effect of increased [K^+] alone (before time zero and extrapolated using exponential function) and after adding SKT.
Figure 5. Experiments showing increased interstitial potassium during human muscle contraction (Green et al 2000).
Figure 6. Computational experiment showing reconstruction of rise in interstitial potassium in the Shorten (2007) model during repetitive contractions.

CONCLUSION

We analysed the result to indicate that potassium is a potent facilitator of the action of SKT. There is no other example so far where potassium can act as such a powerful facilitator through direct effects on a drug-receptor. It is more probable that the effect arises through a systems network of interactions. This example vindicates the Multi-Scale Systems approach.

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References
Green S. et al, 2000, Interstitial and arterial–venous [K^+] in human calf muscle during dynamic exercise: effect of ischaemia and relation to muscle pain. *Journal of Physiology*, **529**, 849-861.
Noble, D, 2008, Claude Bernard, the first systems biologist, and the future of physiology. *Experimental Physiology*, **93**, 16-26.
Noble, D, Sam, C. & Tasaki, KM, 2016. Reduction of Calcium Influx through L-type Calcium Channel by Shakuyaku-kanzo-to (SKT) and one of its Chemical Components, Glycyrrhetic acid (GA). *FASEB J* April 2016 30:lb710.
Sam, C, Terrar, D, Tasaki, K, Noble, D. 2015a. Actions of a multi-component medication, SKT, in skeletal and smooth muscle. *Proceedings of The Physiological Society*, **34**, PC024.
Sam, C, Terrar, D, Noble, P, Tasaki, K, Noble, D. 2015b. Extracellular potassium may potentiate the action of a multi-component medication, SKT, in skeletal muscle. *Proceedings of The Physiological Society*, **34**, PC025.
Shorten et al 2007. A mathematical model of fatigue in skeletal muscle force contraction. *Journal of Muscle Research and Cell Motility*, **28**, 293-313.
Tasaki, K., Tasaki, T., Noble D. 2015. Principles of Systems Biology. The Way Forward in Healthcare *Journal of the Register of Chinese Herbal Medicine*, **12**, 7-12.

Figure 1

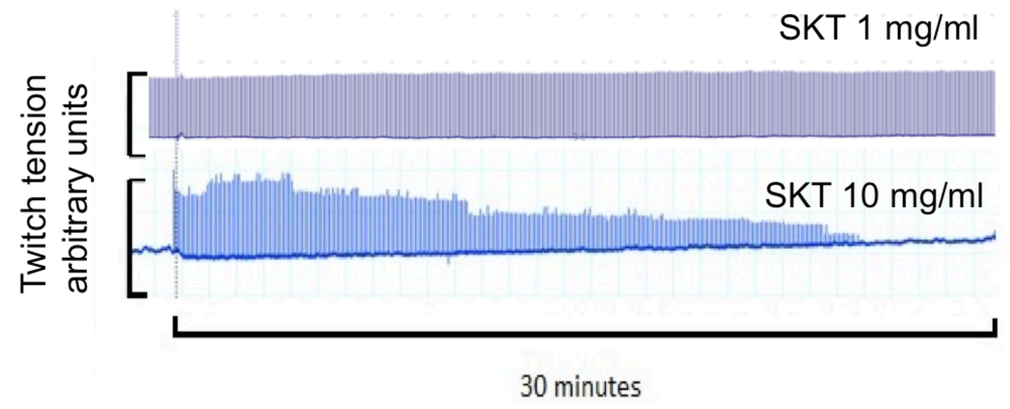

Figure 2

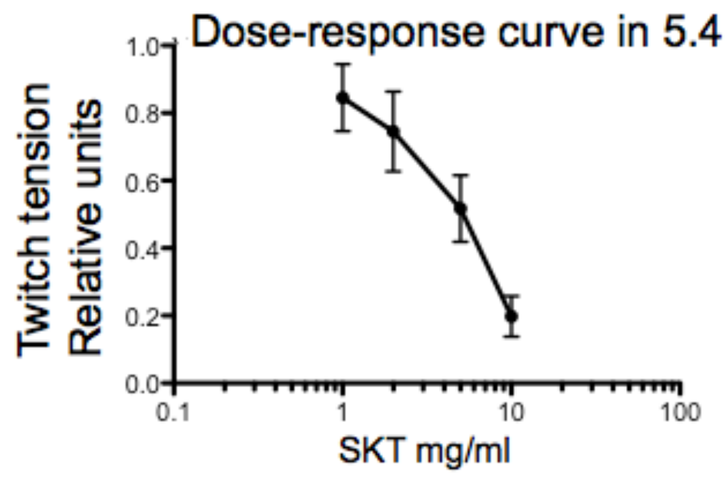

Figure 3

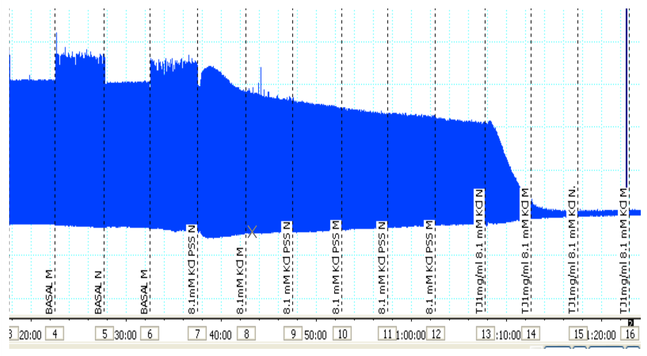

Figure 4

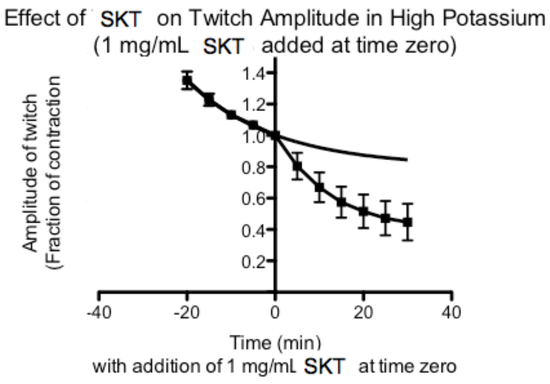

Figure 5

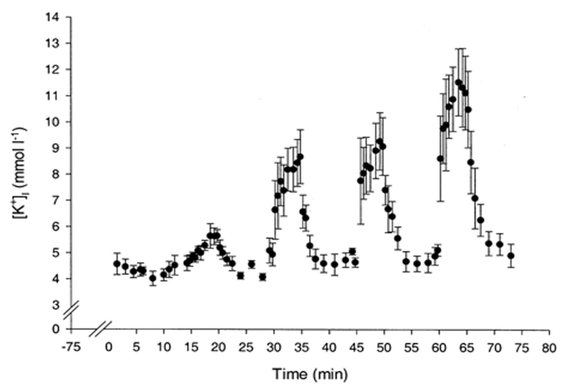

Figure 6