A personal tribute to Johann Caspar Rüegg (1930–2018): milestones of muscle research

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The passing of Caspar Rüegg on 18 January 2018 was met with great sorrow and regret across the scientific community. Muscle physiology and biophysics have lost someone who left his mark on the history of these subjects and who was very popular with colleagues. In grateful memory, we would like to pay tribute to the works and personality of our mentor.

Johann Caspar Rüegg was born on January 28, 1930, in Zürich, Switzerland. After studying medicine in Zürich (MD, 1955) and biochemistry in Cambridge (PhD, 1960), he worked in Heidelberg (“Habilitation,” equivalent to Dr. Sc., 1963), Oxford and Bochum. From 1974 until his retirement in 1998, he was a professor of Physiology at the University of Heidelberg and the Director of the Second Institute of Physiology.

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Rüegg’s mentors and early collaborators included neurophysiologist W.R. Hess (Nobel laureate in 1949) and muscle researchers K. Bailey, H.H. Weber, J.W.S. Pringle, and W. Hasselbach. It was this early interaction that defined Rüegg’s lifelong dedication to muscle research. He often said that it was muscle research that provided groundbreaking knowledge on the functions of living systems, including glycolysis and the role of ATP. Rüegg himself made many groundbreaking discoveries.

Calcium as an intracellular messenger

One of Rüegg’s important contributions to cell biology was his research on the role of intracellular Ca^{2+} in the mid 1960’s. Together with colleagues, he injected Ca^{2+} buffer solutions into giant muscle fibers of crabs while measuring force. These experiments showed how much the Ca^{2+} concentration increases inside muscle cells when stimulated to contract by a neuron (Portzehl et al. 1964). This work unambiguously confirmed Ca^{2+} as an intracellular messenger.

A new preparation for cell biology research

Rüegg was a pioneer in developing new methods for experimental analysis of the interior of cells. His key contribution was the development of “skinned” or “demembranated” muscle cell preparations with the aid of glycerol or detergents (Rüegg and Weber 1963; Jewell et al. 1964). Here, he was able to build on earlier work by Nobel laureate Albert Szent-Györgyi. With the new preparation, it was possible to investigate how ATP-driven rowing motions of the lateral heads of myosin filaments exert force on actin filaments and cause filament sliding.

After this progress in the methods, Rüegg began to study the regulation of the actin-myosin interaction by intracellular Ca^{2+} . Together with colleagues, he was able to measure the

force of skinned skeletal and smooth muscle fiber preparations as a function of Ca^{2+} concentration (Filo et al. 1965).

Skinned muscle fibers offered an opportunity to determine the ATP consumption during contraction. Rüegg and his team used an ingenious technique, in which the ATP hydrolysis was enzymatically coupled to the oxidation of NADH, which was monitored by fluorescence (Griffiths et al. 1980). This technique allowed the ATP hydrolysis rate to be measured during isometric contraction (i.e., at constant muscle length), as well as during shortening.

Variable calcium sensitivity

Over the decades, it became apparent that the effect of Ca^{2+} on the contractile apparatus was not always the same, but was modulated by the degree of stretch (Frank-Starling mechanism in the heart) and by changes in the chemical surroundings of the contractile apparatus. Rüegg and his co-workers found that intracellular inorganic phosphate reduced not only overall muscle strength, but also the Ca^{2+} sensitivity of the contractile apparatus (Herzig and Rüegg 1977). These effects presumably contribute to fatigue when the muscle produces more inorganic phosphate through excessive ATP hydrolysis.

Rüegg's research on the Ca^{2+} sensitivity of the contractile apparatus was pioneering in exploring the role of posttranslational modification of proteins. Together with his team, he found a reduction in Ca^{2+} sensitivity by phosphorylation of the troponin I subunit in the heart (Herzig et al. 1981b). The troponin complex, together with tropomyosin, constitutes the molecular switch that controls the interaction of rowing myosin heads with actin filaments in a Ca^{2+} -dependent manner. Rüegg and his co-workers further observed an increase in Ca^{2+} sensitivity upon phosphorylation of the myosin regulatory light chain, which is bound to the neck region of the myosin head (Morano et al. 1985). These findings demonstrated that heart muscle cells are able to adapt their Ca^{2+} sensitivity to changing physiological requirements.

New heart drugs

Rüegg and co-workers also used skinned muscle preparations to study the influence of synthetic drugs on the contractile apparatus. They found substances that made the contractile apparatus of heart muscle cells more sensitive to Ca^{2+} (Herzig et al. 1981a; Rüegg et al. 1984). These so-called Ca^{2+} sensitizers opened a new possibility of increasing the power of failing hearts without having to raise the intracellular Ca^{2+} concentration, which may be fatal. The Ca^{2+} sensitizer, levosimendan, which was later developed by others, has been in clinical use in many countries for ~15 years.

First phosphatase inhibitor

In similar experiments on smooth muscles, Rüegg and his colleagues found an inhibitor of protein phosphatases, okadaic acid, which is a toxin of marine dinoflagellates. This substance enhanced smooth muscle contraction like a Ca^{2+} sensitizer by inhibiting the dephosphorylation of the myosin heads (Takai et al. 1987). This finding supported the hypothesis that Ca^{2+} regulates smooth muscle contraction via phosphorylation/dephosphorylation of myosin heads. Rüegg and his team also contributed significantly to deciphering the mechanisms of the intracellular messengers cAMP and cGMP in smooth muscle cells (e.g., Herzig et al. 1981b; Pfitzer et al. 1982).

Special contractile phenomena

In addition to his groundbreaking studies on mammalian skeletal, cardiac and smooth muscle cells, Rüegg kept a keen interest in the contractile mechanisms of invertebrate muscles. Using “catch” muscles of mussels, he examined their ability to maintain high force without significant energy consumption. For decades, the catch state was thought to be due to a slowdown of the ATP-driven rowing motions of myosin heads. However, as early as the 1960s, Rüegg inhibited myosin heads with thiourea and observed that the catch state was unaffected (Rüegg 1963). He concluded that the catch mechanism was based on a separate holding structure. This hypothesis was proven to be true more than four decades later, when specific inhibitors of the myosin heads became available (Galler et al. 2005). These studies were of general interest because the smooth muscles of blood vessels also enter into a state of high energy efficiency (“latch” state) when maintaining a contracted state for hours to regulate the blood flow.

Rüegg also investigated asynchronous flight muscles of insects to study their extremely fast oscillatory contractions, which in some cases can produce up to 1000 wing beats per second. Together with colleagues, he was able to demonstrate that skinned fibers of these muscles oscillate spontaneously when they are activated by constant Ca^{2+} concentration (Jewell et al. 1964; Jewell and Rüegg 1966). Consequently, they concluded that the fast contraction-relaxation cycles were not caused by oscillations of the intracellular Ca^{2+} concentration, but were generated by the contractile apparatus itself.

Psychosomatic medicine

Rüegg published his research on the above and other topics in about 190 research articles, 10 review papers and various influential book contributions. In addition to his contribution to muscle physiology, he wrote excellent books on psychosomatic medicine (Rüegg 2011, 2012, 2016) after his retirement.

His main interest was the question of how the brain affects our health. He also discussed whether our thinking alters neuronal circuits of the brain.

Appreciation

Rüegg was awarded the prestigious Adolf Fick Prize of the German Physiological Society, of which he was an honorary member. He was appointed as an Adjunct Professor at the University of Cincinnati (OH, USA) and was Associate Member of the Swiss Academy of Sciences.

Rüegg had acquired extensive knowledge of muscle in his long research career, like hardly any other muscle researcher. He knew the complex muscle field extremely well and recognized the importance of new findings with unequalled perspicacity. His review articles and books demonstrate this remarkable ability (e.g., Rüegg 1971; Rüegg 1992).

Many muscle researchers worldwide have been in personal contact with Rüegg, benefiting directly from his ingenuity and benevolence. He campaigned vehemently for the promotion of young talents and courageously supported colleagues in difficult situations of their careers. Rüegg was certainly not only one of the most excellent of scientists, but also one of the most popular and friendly of muscle researchers.

Every encounter with Caspar was engaging and stimulating. This was also shown on what was presumably his last research visit to a muscle laboratory, at a time when he had long turned to the theoretical work of psychosomatic medicine. At the time, an experiment was being performed on a catch muscle preparation. Rüegg excitedly followed the recording of the force trace and then repeatedly moved between the experimental setup and the tea table while initiating a lively discussion arising from his immense knowledge. When he left, beaming all over his face, he said “Thank you for allowing me to breathe the spirit of muscle research again!”

Thank you, Caspar, for allowing us to breathe your fascinating spirits! Your intellectual heritage lives on in the worldwide muscle community, which you have shaped and enriched hugely.

References

- Filo RS, Bohr DF, Rüegg JC (1965) Glycerinated skeletal and smooth muscle: calcium and magnesium dependence. *Science* 147:1581–1583

- Galler S, Höpfinger MC, Andrichov O, Andrichova O, Grassberger H (2005) Effects of vanadate, phosphate and 2, 3-butanedione monoxime (BDM) on skinned molluscan catch muscle. *Pflügers Arch* 449:372–383
- Griffiths PJ, Güth K, Kuhn HJ, Rüegg JC (1980) ATPase activity in rapidly activated skinned muscle fibres. *Pflügers Arch* 387:167–173
- Herzig and Rüegg (1977) Myocardial cross-bridge activity and its regulation by Ca^{2+} , phosphate and stretch. In: Riecker G, Weber A, Goodwin J (eds) *Myocardial Failure*. Springer, Berlin Heidelberg New York, pp 41–51
- Herzig JW, Feile K, Rüegg JC (1981a) Activating effects of AR-L 115 BS on the Ca^{2+} sensitive force, stiffness and unloaded shortening velocity (V_{max}) in isolated contractile structures from mammalian heart muscle. *Arzneimittel Forsch. Drug Res* 31:188–191
- Herzig JW, Köhler G, Pfitzer G, Rüegg JC, Wölffle G (1981b) Cyclic AMP inhibits contractility of detergent treated glycerol extracted cardiac muscle. *Pflügers Arch* 391:208–212
- Jewell BR, Pringle JWS, Rüegg JC (1964) Oscillatory contraction of insect fibrillar muscle after glycerol extraction. *J Physiol* 173(Suppl):6–8
- Jewell BR, Rüegg JC (1966) Oscillatory contraction of insect fibrillar muscle after glycerol extraction. *Proc R Soc Lond B* 164:428–459
- Morano I, Hofmann F, Zimmer M, Rüegg JC (1985) The influence of P-light chain phosphorylation by myosin light chain kinase on the calcium sensitivity of chemically skinned heart fibres. *FEBS Lett* 189:221–224
- Pfitzer G, Rüegg JC, Flockerzi V, Hofmann F (1982) cGMP-dependent protein kinase decreases calcium sensitivity of skinned cardiac fibres. *FEBS Lett* 149:171–175
- Portzehl H, Caldwell PC, Rüegg JC (1964) The dependence of contraction and relaxation of muscle fibres from the crab *Maia squinado* on the internal concentration of free calcium ions. *Biochim Biophys Acta* 79:581–591
- Rüegg JC (1963) Actomyosin inactivation by thiourea and the nature of viscous tone in a molluscan smooth muscle. *Proc R Soc Lond B* 160:536–542
- Rüegg JC (1971) Smooth muscle tone. *Physiol Rev* 51:201–248
- Rüegg JC (1992) *Calcium in Muscle Contraction: Cellular and Molecular Physiology*, Springer (2nd edition)
- Rüegg JC (2011) *Gehirn, Psyche und Körper*, Schattauer
- Rüegg JC (2012) *Die Herz-Hirn-Connection*, Schattauer
- Rüegg JC (2016) *Mind & Body*, Schattauer
- Rüegg JC, Weber HH (1963) Kontraktionszyklus und Sperrtonus. In: Cori CF, Foglia VG, Leloir LF, Ochoa S (eds) *Perspectives in biology*. Elsevier/North-Holland, Amsterdam, pp 301–320
- Rüegg JC, Pfitzer G, Eubler D, Zeugner C (1984) Effect on contractility of skinned fibres from mammalian heart and smooth muscle by a new benzimidazole derivate [4,5-dihydro-6-2-(4-methoxy-phenyl)-1H-benzimidazol-5-yl]-5-methyl-3(2H)-pyridazinone. (1984). *Arzneim. Forsch. Drug Res* 24:1736–1738
- Takai A, Bialojan C, Troschka M, Rüegg JC (1987) Smooth muscle phosphatase inhibition and force enhancement by black sponge toxin. *FEBS Lett* 217:81–84