HANS-CHRISTOPH LÜTTGAU

20 July 1926 - 5 November 2017

Hans-Christoph Lüttgau was 91 years old when he died in Dortmund on 5th November 2017. He was an outstanding muscle physiologist, best known for his pioneering work on processes that couple the electrical events at the surface membrane in muscle with the release of Ca^{2+} from internal stores and for his work in collaboration with Rolf Niedergerke on Na-Ca antagonism in cardiac muscle, which laid the foundations for the discovery of the ubiquitous Na-Ca exchanger (NCX) in plasma membranes.

Lüttgau was born on 20 July 1926 in Braunschweig (Brunswick), in the German state of Lower Saxony. Between 1937 and 1946, he attended the *Gymnasium* (equivalent to a British grammar school) in the town of Goslar, which was some 20 miles away from his parental home in the village of Göddeckenrode. Whilst still a student at the *Gymnasium*, he was conscripted into the Wehrmacht in June 1944, but was discharged in April 1945 without having been involved in active combat in World War II.

In 1946 he enrolled in the Faculty of Natural Sciences at Georg-August-University in Göttingen, which had been the first German university to resume teaching after the war. He graduated in Natural Sciences in 1949 majoring in Physiology, Zoology and Botany with subsidiary courses in Physics and Chemistry. Between 1949 and 1952 he continued at Göttingen with doctoral studies under the supervision of Prof Hansjochem Autrum, investigating the excitation threshold of myelinated nerve fibres at the node of Ranvier under various experimental conditions. During his

doctoral studies, Lüttgau became proficient at isolating and microdissecting segments of functioning single myelinated nerve fibres, a skill that he later adapted to dissecting intact single skeletal muscle fibres. His interest in the role played by extracellular calcium in maintaining cellular excitability can be traced back to his doctoral studies (Beyer-Gallwitz & Lüttgau, 1953).

The expertise gained in working with single nerve fibres was crucial for Lüttgau in securing the position of *Assistent* (equivalent to a junior Lectureship at a British university) at the Institute of Physiology at the University of Bern, which at that time was led by Professor Alexander von Muralt. The Institute had a high international reputation in neuro- and muscle physiology. It was known as the *Hallerianum* after Albrecht von Haller (1708-77), a native of Bern widely regarded as one of the founders of experimental physiology. Lüttgau was associated with the Hallerianum between 1954 and 1967 and greatly benefited not only from the advanced research opportunities at the Institute, but also from the close ties with the newly-founded Department of Biophysics at University College (UCL) in London and the Physiological Laboratory in Cambridge.

In Bern, Christoph Lüttgau initially focused his investigations on the effects of UV light on the excitation process in myelinated nerve fibres. He showed that the Na^+-channels were particularly sensitive to UV light, which reduces their conductivity, as compared with the K^+-channels (Lüttgau, 1956). During this time, he was mentored by Silvio Weidmann as he expanded his knowledge of excitable cell biophysics. At the invitation of Bernard Katz, who was Head of the Department of Biophysics at UCL, he took up an Honorary Research Assistant position for one year in 1956 on a stipend from the University of Bern organised by von Muralt. At UCL, he was assigned to work with Rolf Niedergerke whom he already knew from Göttingen. Their experiments were designed to examine the way in which the strength of contraction of frog cardiac muscle is influenced by the Ca-Na antagonism. (That phenomenon had first been described by Willbrandt and Koller from the Hallerianum in the 1940s where Niedergerke had also worked briefly, prior to 1951). The idea of a common mechanism at which Ca^{2+} and Na^+ ions competed antagonistically for their inward movement arose from their results, published in 1957 and 1958. The algebraic description of this receptor-based antagonism in the 1958 paper was further developed, in part from an exchange of letters between Alan Hodgkin and Rolf Niedergerke. Hodgkin had broken his anonymity as the referee for the 1958 *Journal of Physiology* paper and suggested a way in which the voltage-sensitivity of Ca-Na antagonism could be described in explicit terms, adding ‘‘I expect you have been considering much of this already’’ (Hodgkin 1958). This model of voltage sensitivity, which goes beyond the 1958 formalism, was detailed by Lüttgau at a meeting in 1963 in Milan (Lüttgau, 1965a).

This theme was to be extended and refined first by Harald Reuter (Christoph’s cousin) and Norbert Seitz working on guinea-pig heart (1968) and then by Peter Baker, Mordecai Blaustein, Alan Hodgkin and Richard Steinhardt, working on the squid axon (1969). These authors showed that the inward movement of calcium is coupled to the outward movement of sodium and *vice versa*. The Na-Ca exchanger (NCX) is now known to be one of the most important cellular

mechanisms for keeping the intracellular Ca^{2+} concentration very low, an essential pre-requisite for the regulation of many cellular mechanisms and thus for cellular function in general.

After his return to Bern from UCL, Lüttgau continued his work on myelinated nerve fibres. The generation of abnormal action potentials in nerve fibres in Na-free, K-rich solutions had been presented in the literature as evidence against the Ionic Theory of excitation formulated by Hodgkin and Huxley. However, the experiments conducted by Lüttgau provided evidence that these abnormal action potentials arise from potassium ions moving down their electrochemical gradient following the regenerative increase of potassium permeability, as predicted by the Ionic Theory of excitation (Lüttgau 1959, 1960). As such, this work represents an important contribution in showing that these abnormal action potentials do not contradict the Ionic Theory of excitation, but, to the contrary, are actually explained by it.

After his *Habilitation* at the end of 1959 (a process common in German-speaking countries in which the scientific achievements of a postdoctoral candidate, together with their teaching ability, are assessed by a panel of experts) and promotion to *Oberassistent* (equivalent to Senior Lecturer at a British University) at the Hallerianum in 1961, Lüttgau changed the focus of his research from nerve to skeletal muscle. During his stay at UCL, he had become familiar with research conducted by Rolf Niedergerke on single skeletal muscle fibres. Based on their work on cardiac Na-Ca antagonism, Lüttgau became interested in the role of extracellular Ca in excitation-contraction coupling in skeletal muscle.

Work started in Bern on the effects of extracellular Ca^{2+} on high K^{+}- (*i.e* depolarisation-induced) contractures in frog single skeletal muscle fibres, was continued in the Physiology Laboratory at Cambridge, where Lüttgau spent one year in 1962-3 at the invitation of Alan Hodgkin, and later at the Ruhr University in Bochum, where he was to be appointed the Founding Head of the Department of Cell Physiology in 1967. This important body of work (Lüttgau, 1963, Lüttgau & Spiecker, 1979, Spiecker *et al* 1979*,* Schnier *et al* 1993) has put to rest a major controversy in muscle research by conclusively showing that, unlike the situation with cardiac muscle, a Ca^{2+}-influx was not necessary for the initiation of muscle contraction in skeletal muscle. The results however, also showed that a decrease of extracellular Ca^{2+} concentration shifts the voltage-dependent inactivation curve in skeletal muscle towards more negative potentials (Lüttgau, 1963, Schnier *et al* 1993), such that the voltage sensors become inactivated at resting levels of the membrane potential when the extracellular Ca^{2+} concentration is reduced to below 100 nM. Thus, while an influx of extracellular Ca ions is not needed to initiate contraction in skeletal muscle, the presence of Ca^{2+} at an external site is nevertheless necessary for eliciting contraction. The last paper in this series (Schnier *et al* 1993), which proved to be Lüttgau's last experimental paper, also offers a quantitative explanation of these observations based on the concept developed by Eduardo Rios and colleagues (Pizzaro et al, 1989; Rios & Pizzaro, 1991) concerning the state-dependent binding of a metal cation such as Ca^{2+} to an external binding site on the voltage sensor.

After his return to Bern from Cambridge, Lüttgau was promoted in 1964 to *Extraordinarius* in Physiology, roughly equivalent to a Readership position at a British University. A particularly important contribution to muscle research made by him at that time was the introduction of caffeine and tetracaine as valuable tools in the study of excitation-contraction coupling. His paper with Hans Oetlicker (1968) was the first systematic investigation of the effects of caffeine and tetracaine on the membrane potential dependence of contractile activation and inactivation of intact muscle fibres. More than any other paper from that time, this work has created the impetus for the intense study of the (then) very poorly understood mechanism of excitation–contraction (EC) coupling in skeletal muscle. For example, in 1967, when the paper was written, there was no knowledge on the existence of the two major protagonists involved in signal transmission from the transverse tubular (t-) membrane to the intracellular Ca^{2+} stores: the dihydropyridine receptors (DHPRs)/voltage sensors in the membrane of the t-system and the ryanodine receptors (RyRs)/Ca^{2+} release channels of the sarcoplasmic reticulum (SR). Caffeine opens the RyRs while procaine blocks their opening. Caffeine, in particular, continues to be used as a versatile tool in muscle research and in clinical diagnosis for determining patient susceptibility to medical conditions such as malignant hyperthermia (Herrmann-Frank, Lüttgau & Stephenson, 1999).

Lüttgau has also made major contributions towards the characterisation of processes that occur in muscle fatigue, particularly with respect to electrical events at the surface membrane. He developed an interest in this area of research during his first visit to Cambridge in 1962-3, focused on this topic during his second visit there in 1964 (Lüttgau*,* 1965b). He was much influenced by his time in Hodgkin's laboratory where he extended his work on isolated single skeletal muscle fibres. One anecdote of Christoph's from that time is illuminating. He had just finished a first draft of one of his papers and gave it to Hodgkin to look through. When he went to pick it up again, he was very disappointed by the many remarks (not only grammatical) he found on the paper. Hodgkin recognized his anger, said to him "Yes, we all are ready to be corrected, but we don't want to be criticised". This comment has made a lasting impression on Christoph, who many years later was very proud to announce when a paper was accepted for publication in the *Journal of Physiology* without modification.

Lüttgau continued experiments on muscle fatigue after his move to the Ruhr University in Bochum in 1967 (Grabowski et al 1972, Fink & Lüttgau 1976, Fink *et al* 1983, Lüttgau & Wettwer 1983). Based on this research, we now know that (i) muscle fatigue at high frequency of stimulation (> 50 Hz) is caused by a decrease in amplitude, followed by failure of action potentials (due to inactivation of Na^{+}-channels caused by K accumulation in the t-system), (ii) there is a massive decrease in membrane resistance in metabolically-exhausted muscle fibres due to the increase in K conductance associated with a rise in intracellular Ca^{2+} and depletion of energy stores and (iii) caffeine can restore the force response in fatigued fibres by facilitating the release of Ca^{2+} from the SR.

After taking up the position of Founding Chair in Cell Physiology in 1967 at the newly established Ruhr University in Bochum, Germany (then still West Germany) his main concern was to fill 'the infinitely many rooms [in the Department] with scientific life'. He recruited Caspar Rüegg and his collaborators, followed by Helfried Glitsch and his group, when Caspar Rüegg took the Chair of the 2nd Department of Physiology at the University of Heidelberg in 1973. (Caspar Rüegg, who died on 18th January 2018, had been for many years Editor of the Journal of Muscle Research and Cell Motility). Under Lüttgau's stewardship, the Department of Cell Physiology at Ruhr University became one of the most influential muscle research centres in Germany.

As an experimental physiologist, Lüttgau was accustomed to working in small groups, in which, according to the Cambridge model, he was directly involved in selecting the topic, the design of experiments, collection of data, analysis of results and manuscript preparation for publication. At the Ruhr University, he continued to follow the Cambridge model by organising people to work in small groups, being supportive of his students and younger members of staff and maintaining a high ethical and moral standard by never having his name on publications originating from his Department if he was not directly involved in the design, execution and analysis of results. The Cell Physiology Department at Ruhr University in Bochum was a happy and stimulating place to be and the two of us (DGS and DJM) greatly benefited from Lüttgau's leadership and support when we were working in that environment as young UK-trained postdocs in the 1970s.

New areas of research pursued by Lüttgau at the Ruhr University refer to the action of perchlorate (Gomolla *et al* 1983, Lüttgau *et al* 1983, Feldmeyer & Lüttgau, 1988) and Ca^{2+}-antagonists (Berwe *et al* 1987, Erdmann & Lüttgau, 1989, Neuhaus *et al* 1990, Böhle 1992) on excitation-contraction coupling. The specific and parallel effects of perchlorate on the membrane potential dependence of force activation and intramembrane charge movement, together with the lack of effect on the membrane potential dependence of force inactivation and Na^{+}- and K^{+}-channels supported the hypothesis that the charge movements associated with the DHP-receptors in the t-system membrane are directly responsible for the activation of the RyRs through which Ca^{2+} is released from the SR to activate contraction. The specific effects of perchlorate on different events in the excitation-contraction coupling has generated considerable interest in the field prompting the use of perchlorate as a valuable tool to investigate specific aspects of excitation–contraction coupling in skeletal muscle.

The so-called Ca^{2+}-antagonists are substances that bind with high affinity to the voltage sensors in the tubular membrane of skeletal muscle fibres following the depolarisation-induced transition from the resting, to the active and then inactive states, causing dissociation of extracellular Ca^{2+} from the voltage sensors and stabilization of the voltage sensors in the inactivated state. Some Ca^{2+}-antagonists promote further transition into a secondary inactive state, called the paralysed state, from which they recover slowly after membrane hyperpolarisation. Lüttgau's laboratory had performed the first truly quantitative analyses of the action of several Ca^{2+}-antagonists D600 (galopamil), D888 (devapamil), nifedipine and diltiazem. These drugs are used in the treatment

of various cardiac disorders and can also become important tools for the better understanding of events occurring in the early stages of the excitation-contraction coupling in skeletal muscle.

Christoph Lüttgau became Professor Emeritus in 1991 after retiring as Head of the Cell Physiology Department. During his academic career, he supervised and trained 17 doctoral students, many of whom went to take university academic positions. In 1993 he published his last experimental paper in the *Journal of Muscle Research and Cell Motility* (Schnier *et al*, 1993) in which, as mentioned before, the Ca^{2+} ion binding site at the voltage sensor is characterised. In 1995 he published a most influential and highly cited review on the role of Ca^{2+}-ions in excitation-contraction coupling of skeletal muscle fibres with two of his former doctoral students, Werner Melzer and Annegret Hermann-Frank, and in 1999 he wrote another review on the use of caffeine as a tool in muscle research together with Annegret Hermann-Frank and one of us (DGS). He also wrote insightful biographical memoirs (in German) of: Alan Hodgkin (2000), Bernard Katz (2001), Silvio Weidmann (2006) and Andrew Huxley (2013). He collaborated with one of us (DJM) on an obituary of Rolf Niedergerke for *Physiology News* (2012). The article on Andrew Huxley was co-authored by Rolf Thieleczek, one of his former doctoral students, with whom he stayed in regular contact until the very end of his life, as did we both and several others.

Hans-Christoph Lüttgau was always a reflective and thoughtful man with a dry sense of humour. In later years, he addressed questions of philosophy and religion, most notably in 2009 when he prepared two lectures for a (biologically) lay audience to mark the 200th anniversary of Darwin's birth and the 150th of the publication of '*On the Origin of Species'*. He was very close to his two sons, Bernhard and Philipp, and his four grandchildren. His mind stayed clear to the end. He followed with interest the scientific literature, for new developments, which he enjoyed discussing on a regular basis with several of his former students and colleagues with whom he maintained regular contact.

Like many fellow-citizens of his generation, he was also full of remorse and criticism for the injustices and atrocities perpetrated by Nazi Germany. He was humbled by the support given to him and other German scientists after the war by people who have suffered at the hands of that regime.

Hans-Christoph Lüttgau will be remembered as a great scientist, a major figure in muscle physiology for his pioneering work in the field of excitation-contraction coupling and as a great mentor who lead by example his postgraduate students and younger colleagues.

This article expands on an obituary first published in Physiology News.

D George Stephenson & David J Miller

References

Baker, P.F., Blaustein, M.P., Hodgkin, A.L. & Steinhardt, R.A. (1969). The influence of calcium on sodium efflux in squid axons. *J Physiol* **200**, 431-458.

Berwe D, Gottschalk G & Lüttgau HC (1987) Effects of the calcium antagonist gallopamil (D600) upon excitation-contraction coupling in toe muscle fibres of the frog. *J Physiol*, **385**, 693-705.

Beyer-Gallwitz U & Lüttgau HC (1953) Unterschwellige Erregbarkeitsänderungen isolierter markhaltiger Nervenfasern nach Calciumentzug. *Naturwiss* **40,** 366-367.

Erdmann R & Lüttgau HC (1989) The effect of the phenylalkylamine D888 (devapamil) on force and Ca2+ current in isolated frog skeletal muscle fibres. *J Physiol*, **413**, 521-541.

Feldmeyer, D. & Lüttgau, H.C. (1988) The effect of perchlorate on Ca currents and mechanical force in skeletal muscle fibres. *Pflügers Arch*, **411**, R190.

Fink, R., Hase, S., Lüttgau, H.C. & Wettwer, E. (1983) The effect of cellular energy reserves and internal calcium ions on the potassium conductance in skeletal muscle of the frog. *J Physiol* **336**, 211-228.

Fink, R. & Lüttgau, H.C. (1976) An evaluation of the membrane constants and the potassium conductance in metabolically exhausted muscle fibres. *J Physiol* **263**,215-238.

Gomolla, M., Gottschalk, G. & Lüttgau, H.C. (1983) Perchlorate-induced alterations in electrical and mechanical parameters of frog skeletal muscle fibres. *J Physiol* **343**, 197-214.

Grabowski, W., Lobsiger, E.A. & Lüttgau, H.C. (1972) The effect of repetitive stimulation at low frequencies upon the electrical and mechanical activity of single muscle fibres. *Pflügers Arch*, **334**, 222-239.

Herrmann-Frank, A., Lüttgau, H.C. & Stephenson, D.G. (1999) Caffeine and excitation–contraction coupling in skeletal muscle: a stimulating story. *J Muscle Res Cell Motil*, **20**, 223-237.

Hodgkin AL (1958) Text quoted from a letter from ALH to R Niedergerke, 24 April 1958: copy provided to us by H-Ch Lüttgau

Lüttgau, H.C. (1956) Elektrophysiologische Analyse der Wirkung von UV-Licht auf die isolierte Markhaltige Nervenfaser *Pflügers Archiv* **262**, 244-255.

Lüttgau, H.C. (1959) Action potentials from single nodes of Ranvier in potassium-rich solutions. *Nature*, **184**, 1494-1495.

Lüttgau, H.C. (1960) Das Kalium-Transportsystem am Ranvier-Knoten isolierter markhaltiger Nervenfasern. *Pflügers Archiv*, **271**, 613-633.

Lüttgau, H.C. (1963) The action of calcium ions on potassium contractures of single muscle fibres. *J Physiol*, **168**,679-697.

Lüttgau H-Ch (1965a) The role of calcium ions in excitation- contraction coupling in myocardium. In: Marchetti G (ed) *Electrophysiology of the heart* (Milan 1963) *pp* 87-95 Taccardi B. Pergamon Press, London

Lüttgau, H.C. (1965b) The effect of metabolic inhibitors on the fatigue of the action potential in single muscle fibres. *J Physiol*, **178**, 45-67.

Lüttgau, H.C. (2000) Alan Lloyd Hodgkin (1914-1998), *Naturwiss Rundschau* **53**, 341-348

Lüttgau, H.C. (2001) Bernard Katz (1911-2003), *Naturwiss Rundschau* **54**, 132-139

Lüttgau, H. C. (2006).-Silvio Weidmann (1921-2005)--Die Anfange der modernen zellularen Herzelektrophysiologie. *Naturwissenschaftliche Rundschau*, ***59***, 360-369.

Lüttgau H.C. & Böhle, T. (1992) The effect of the benzothiazepine diltiazem on force and Ca2+ current in isolated frog skeletal muscle fibres. *J Physiol*, **445**, 303-318.

Lüttgau, H.C. & Miller, D.J. (2012) Rolf Niedergerke 1921-2011. *Physiology News* **87***,* 44.

Lüttgau, H.C. & Niedergerke, R. (1957) Antagonism between calcium and sodium ions. *Nature*, **179**, 1066-1067.

Lüttgau, H.C. & Niedergerke, R. (1958) The antagonism between Ca and Na ions on the frog's heart. *J Physiol*, **143**, 486—505.

Luttgau, H.C. & Oetlicker, H. (1968) The action of caffeine on the activation of the contractile mechanism in striated muscle fibres. *J Physiol*, **194**, 51-74.

Lüttgau, H.C. & Spiecker, W. (1979) The effects of calcium deprivation upon mechanical and electrophysiological parameters in skeletal muscle fibres of the frog. *J Physiol* **296**, 411-429.

Lüttgau, H.C. & Thieleczek, R. (2013) Andrew Fielding Huxley (1917–2012) Teil 1: Der Weg zur Ionentheorie der Erregung *Naturwiss Rundschau* **66**, 238-247.

Lüttgau, H.C. & Thieleczek, R. (2013) Andrew Fielding Huxley (1917–2012) Teil 2: A. F. Huxleys Beiträge zur Aufklärung des Kontraktionsmechanismus des Skelettmuskels – Paradigmenwechsel in der Muskelforschung. *Naturwiss Rundschau* **66**, 293-302.

Lüttgau, H.C. & Wettwer, E. (1983) Ca2+-activated potassium conductance in metabolically exhausted skeletal muscle fibres. *Cell Calcium* **4**, 331-341.

Lüttgau, H.C., Gottschalk, G., Kovács, L. & Fuxreiter, M. (1983) How perchlorate improves excitation-contraction coupling in skeletal muscle fibers. *Biophys J*, **43**, 247-249.

Melzer, W., Herrmann-Frank, A. & Lüttgau, H.C. (1995) The role of Ca^{2+} ions in excitation-contraction coupling of skeletal muscle fibres. *Biochim. Biophys. Acta*, **1241**, 59-116.

Neuhaus, R., Rosenthal, R. & Lüttgau, H.C. (1990) The effects of dihydropyridine derivatives on force and Ca2+ current in frog skeletal muscle fibres. *J Physiol*, **427**, 187-209.

Pizarro G, Fitts R, Uribe I & Rios E (1989). The voltage sensor of excitation-contraction coupling in skeletal muscle. Ion dependence and selectivity. *J. Gen. Physiol.* **94**, 405-428.

Reuter, H. & Seitz, N. (1968) The dependence of calcium efflux from cardiac muscle on temperature and external ion composition. *J Physiol*, **195**, 451-470.

Rios, E. & Pizarro, G. (1991) Voltage sensor of excitation-contraction coupling in skeletal muscle. Physiol Rev 71, 849-908.

Schnier, A., Lüttgau, H.C. & Melzer, W (19.93) Role of extracellular metal cations in the potential dependence of force inactivation in skeletal muscle fibres. *J Muscle Res Cell Motil*, **14**, 565-572.

Spiecker, W, Melzer, W. & Lüttgau, H.C. (1979) Extracellular Ca^{2+} and excitation–contraction coupling**.** *Nature* **280**, 158-160.