THE ROYAL SOCIETY

Published online 3 March 2003

The discovery of long-term potentiation

Terje Lømo

Department of Physiology, University of Oslo, P.O. Box 1103, Blindern, 0317 Oslo, Norway (*terje.lomo@basalmed.uio.no*)

This paper describes circumstances around the discovery of long-term potentiation (LTP). In 1966, I had just begun independent work for the degree of *Dr medicinae* (PhD) in Per Andersen's laboratory in Oslo after an eighteen-month apprenticeship with him. Studying the effects of activating the perforant path to dentate granule cells in the hippocampus of anaesthetized rabbits, I observed that brief trains of stimuli resulted in increased efficiency of transmission at the perforant path-granule cell synapses that could last for hours. In 1968, Tim Bliss came to Per Andersen's laboratory to learn about the hippocampus and field potential recording for studies of possible memory mechanisms. The two of us then followed up my preliminary results from 1966 and did the experiments that resulted in a paper that is now properly considered to be the basic reference for the discovery of LTP.

Keywords: long-term potentiation; hippocampus; history of long-term potentiation; memory mechanisms

The discovery of LTP, as far as I am concerned, began in 1964. I was a doctor in the Norwegian Navy on leave to look for a job, when, by pure chance, I met Per Andersen in a street in Oslo. Per had recently returned from John Eccles' laboratory in Australia and was looking for people to work in his laboratory. Without that meeting, I would almost certainly not have ended up in neuroscience. As it was, I joined Per's laboratory in August 1964. Before then, I had spent a year at The Institute of Physiology in Pisa, Italy (1958–1959) and was therefore not completely naive in matters of research (Lømo & Mollica 1962).

I worked closely with Per for over a year, learning all that I needed to know to begin my own studies for a PhD (Dr medicinae) in his laboratory at the end of 1965. In those days, a PhD was expected to reflect essentially completely independent work and this suited me well. I needed to know that I could get along on my own. In 1969, I defended my thesis entitled 'Synaptic mechanisms and organization in the dentate area of the hippocampal formation', based on four single-author papers. The four papers were submitted to the journal *Experimental Brain Research* and two were published there (Lømo 1971*a*,*b*). The other two remain in my files unrevised and unrevisited. Because I believe that these papers still contain original and interesting observations, I want to modify them for eventual re-submission. They deal mainly with the longitudinal spread of excitation and inhibition on either side of a narrow transverse beam of excitation of dentate granule cells in the living animal. Subsequently, the *in vitro* transverse slice preparation conquered the field and, not many similar studies have been done.

Per and I agreed that my thesis should focus on 'frequency potentiation', a marked increase in neuronal firing that occurs during repetitive stimulation of axonal inputs. Frequency potentiation had already been described by Per in the perforant path input to the dentate area as a process 'requiring several seconds of tetanic stimulation to make itself manifest (and) conversely, after cessation of the tetanus, as a state of increased excitability of the granule cells lasting several seconds, sometimes for as long as half a minute' (Andersen *et al.* 1966, p. 457).

I began by recording field potentials in dendritic and cell body layers of the dentate area during repetitive stimulation of the perforant path and was impressed not only by the recruitment of cell discharges but also by the marked direct current shifts of different polarities that occurred in different layers. Soon, I also began looking for after-effects of repetitive stimulation, which were generally reported as short lasting (minutes) and akin to PTP (Green & Adey 1956; Gloor *et al.* 1964). PTP lasting hours was observed in the spinal cord but only after prolonged, high-frequency stimulation. Eccles (1964) and Kandel & Spencer (1968) discussed such after-effects as expressions of synaptic plasticity but not as possible mechanisms of learning (Eccles 1964; Kandel & Spencer 1968). Thus, Eccles writes: 'Perhaps the most unsatisfactory feature of the attempt to explain the phenomena of learning and conditioning by the demonstrated changes in synaptic efficacy is that long periods of excess use or disuse are required in order to produce detectable synaptic change', p. 260.

I presented my findings in Åbo (Turku, Finland) in August 1966 at a meeting of the Scandinavian Physiological Society (Lømo 1966). Figure 1 is a copy of the only slide that I still have and can remember that I presented at that meeting. Figure 1*a* shows recordings from the granule cell body layer during trains of stimuli at 12 Hz to the perforant path. The marked increase in amplitude and number of population spikes during each train is typical of frequency potentiation. In this experiment, trains of 120 pulses were delivered every 7 min except for the last two trains, which were separated by 22 min. For each new

One contribution of 30 to a Theme Issue 'Long-term potentiation: enhancing neuroscience for 30 years'.

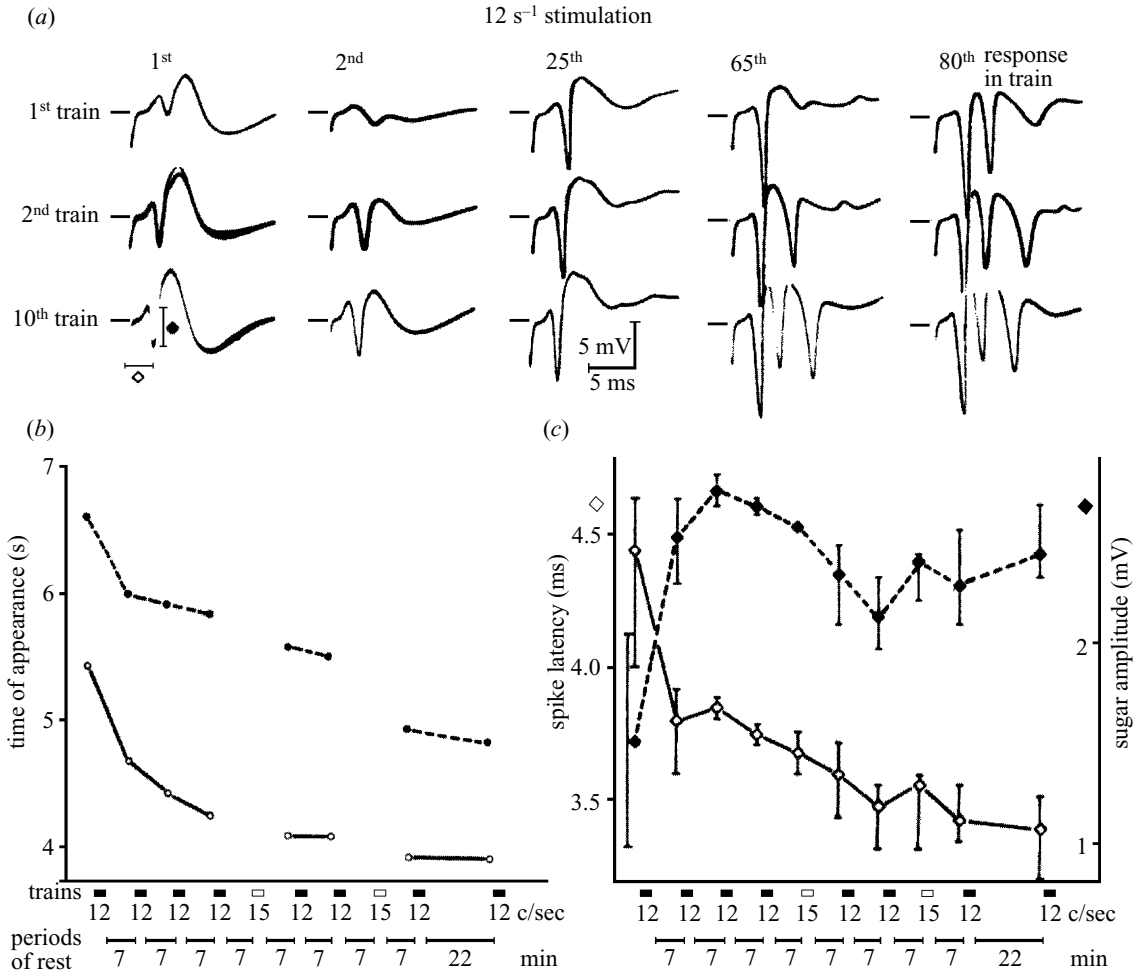

Figure 1. Long-lasting increases in efficiency of transmission at synapses on dentate granule cells induced by repetitive trains of stimuli to the perforant path in anaesthetized rabbits. (*a*) Typical records of population spikes from the granule cell body layer during trains of stimuli at 12 Hz, each train lasting 10 s and repeated as indicated along the abscissa in (*b*) and (*c*). As the trains were repeated, a second and third population spike appeared earlier and earlier in each train ((*a*) and (*b*)). In addition, long-lasting decreases in latency and increases in amplitude appeared in the population spike evoked by single test stimuli before each train (*c*). In (*b*) dashed line, time of appearance of two spikes; solid line, time of appearance of three spikes. In (*c*) dashed line, spike amplitude (single volley); solid line, spike latency (single volley).

train, the second and third population spike in each discharge appeared earlier and earlier in the train (figure 1*a*,*b*). In addition, the amplitude of the monosynaptic first spike increased rapidly to a new maintained potentiated level, while its latency decreased progressively to a new and apparently stable low level (figure 1*c*).

Per and I were excited by these findings. In a paper prepared for a meeting in 1965 (but published in 1967) Per (with me as co-author) discussed a 'possible relationship between frequency potentiation and learning processes' in the following terms: '…the increase in EPSPs denoting an enhanced efficiency of synaptic transmission outlasts the stimulation by a certain period, from several seconds up to a few minutes. This duration is of the same order of magnitude as that of the post-tetanic potentiation. It is too short to account for the plastic changes in a neuronal circuit that might take place in learning processes of a higher kind. However, if frequency potentiation takes place in a set of neurons constituting a polysynaptic chain, the individual effects may be greatly enhanced…' (Andersen & Lømo 1967, p. 410).

By results such as those shown in figure 1, a possible relationship between frequency potentiation, its aftereffects, and learning processes suddenly appeared much more likely. Further evidence that we thought so at the time is provided by Tim Bliss, who recollects that when he approached Per in the winter of 1967–1968 about coming to Oslo to learn about the hippocampus and field potential recording because of his continuing interest in the neural basis of learning and the conviction that he needed to work on a simpler brain structure, Per said something like 'well in that case you must come to Oslo and see what Terje Lømo has found' (T. Bliss, personal communication).

Why did I not pursue and publish a fuller account of my findings in 1966? Because I was overcome by the complexity of the system and my lack of understanding of what was behind the findings. There was also no sense of urgency. Thus, when Tim and I published a full account in 1973 (Bliss & Lømo 1973), it still took years for the significance of the findings to be generally appreciated. To understand the system better, I therefore switched from

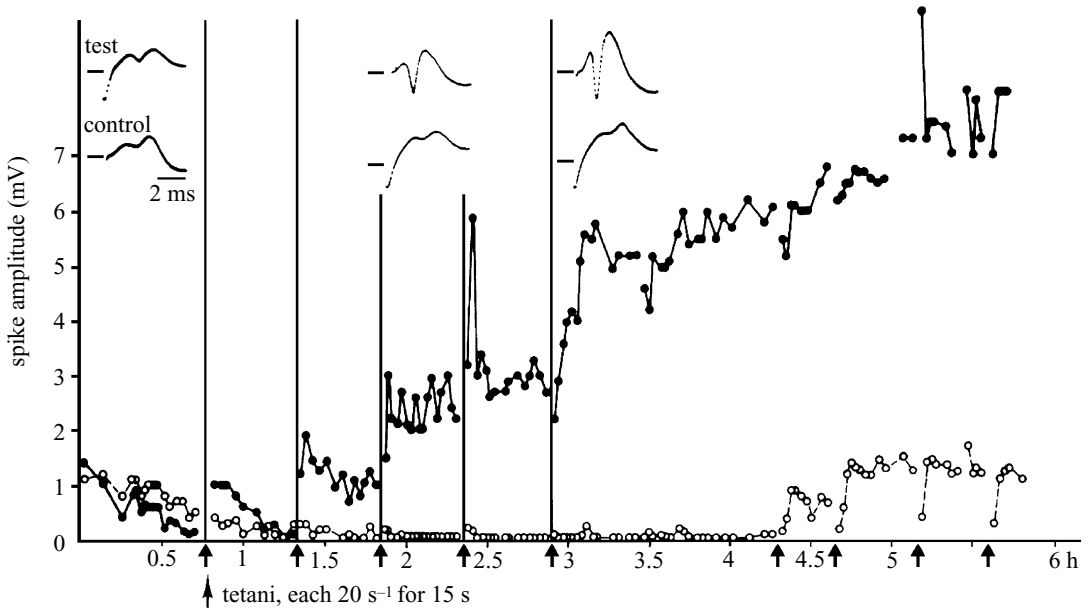

Figure 2. Long-lasting increases in efficiency of transmission at synapses on dentate granule cells induced by repetitive trains of stimuli to the perforant path in anaesthetized rabbits. Insets show responses in the granule cell body layer to single test stimuli to the perforant path at times corresponding to their positions along the abscissa. Trains of stimuli at 20 Hz for 15 s were applied (arrows), first on one side (five trains) then on the opposite side (four trains). The trains caused an increase in the amplitude (and a decrease in the latency) of the population without affecting the contralateral control side. Furthermore, the changes persisted for the duration of the acute experiment.

studying frequency potentiation and its after-effects to studying single and paired pulse activation of orthodromic and antidromic inputs to the dentate area in combination with field potential and some intracellular recordings. This last work resulted in a relatively detailed description of the time-courses and spatial distributions of activity-induced excitability changes in the dentate area, which I presented in the thesis that I defended in October 1969 just before I left to do postdoctoral work for one and half years at the Department of Biophysics, University College London. The study of frequency potentiation, which started me off, produced a fair amount of data, some of which I could probably recover but hardly publish today. With respect to the long-term after-effects of frequency potentiation, however, the arrival of Tim Bliss in Oslo in the autumn of 1968 made all the difference. Furthermore, by that time, I had acquired the experience and insight into the system that I felt was required.

When Tim arrived, we decided to carry out experiments together once a week on 'my' set-up to follow up on the findings presented in Åbo in 1966. The first experiment was immensely exciting. As shown in figure 2, each train of stimuli to the perforant path (tetanus at time of arrows) resulted in a progressive increase in the amplitude of the population spike of discharging granule cells on the tetanized side. By contrast, on the opposite control side, no potentiation occurred until that side was similarly tetanized at the end of the experiment late at night.

We then refined various technical aspects and did our last experiment in September 1969 before we both moved to London. The results, as mentioned, appeared in the *Journal of Physiology* in 1973. The reasons for the delay in publication are many. Again, the sense of urgency was nothing like what it would have been today. The time to think things over was longer then, which seemed to be confirmed by the relative lack of enthusiasm expressed by most people upon hearing the results. John Eccles was an exception. He became very interested when he saw the results during a visit to Oslo in 1968–1969 and presented variations of figure 2, which we never published, in several of his later books. There was also much analysis to be done, some of which had to await my return to Oslo in 1971, where the records were.

An intriguing but unanswerable question, of course, is if not me, then who would have discovered the long-lasting after-effects described above and when would that have happened? Certainly, Per Andersen set the scene for it all and appreciated its significance as a potential memory mechanism early. He has also been remarkably supportive in projecting me as the 'discoverer' of LTP from the beginning. Tim Bliss came to Oslo with the explicit aim of learning the hippocampus and studying potential memory mechanisms in a simpler cortical preparation than the one he had used in Montreal and London (Bliss *et al.* 1968). Thus, in the introduction to Bliss *et al.* (1968) it is made very clear that the intention of the work is to look for long-lasting facilitation of cortical synapses that might underlie learning. Without Tim's arrival in Oslo it is not clear when, if at all, I, or Per, would have followed up the findings reported in Åbo in 1966. As for me, it was certainly not prior interest in possible memory mechanisms that led me to a discovery that was in some ways accidental and in other ways the result of an intuition that has often, I feel, brought me to look for or see phenomena that turn out to be new and interesting.

I find it remarkable that the abstract from the Åbo meeting is sometimes cited for the discovery of LTP. This would hardly have happened, had not the introduction to Bliss & Lømo (1973) started 'These experiments arose from an observation made during a study of the phenom-

enon of frequency potentiation in the dentate area of the hippocampal formation' (Lømo 1966, p. 128). From the literature, it is clear that the phenomenon that I presented in 1966 represented something entirely new. It led directly to Bliss & Lømo (1973), of which Roger Nicoll has said: 'Why did this paper start this dramatic field? First of all, it describes all of the basic phenomena of the process of long-term potentiation. These include pathway specificity, saturation, and an increase in the coupling of the synaptic potential to the discharge of the granule cells. Second, there's not a single controversial result in that paper—a very remarkable thing in this field' (Bliss & Lømo 1995, p. 61).

Why did I not continue studying LTP? In fact, I did, first with Tim in London and then, after London, with Tony Gardner-Medwin in 1971–1972 in Oslo. However, we all failed in bringing the highly variable *in vivo* or *in vitro* preparations under such experimental control that we could fruitfully address underlying mechanisms. Tim left the LTP field for a time, while I returned to and then stayed with the nerve–muscle preparation that had given such wonderful and unexpected results in London.

Up until 1972 it was generally thought that motor neurons controlled the properties of skeletal muscle fibres outside the neuromuscular junctions by nerve-derived trophic factors that acted independently of impulse activity. According to Eccles (1964), the evidence for such factors was even conclusive. However, when we showed that direct muscle stimulation restored normal properties in denervated muscle with regard to acetylcholine sensitivity and resting membrane potential and mimicked the effects of cross-reinnervation on contractile speed, that view was turned upside down (Lømo & Rosenthal 1972; Lømo *et al*. 1974). Moreover, in the early 1970s, these results attracted much greater interest than LTP.

Do I regret that I left the LTP field? Not at all. For me, gaining new insights into how motor neurons set up neuromuscular junctions and control muscle cell phenotype has the same intrinsic value as similar work in other systems and excites me just as much. I like discovering new land, as occurred in the experiments on muscle referred to above or most recently when Gabriela Bezakova discovered that denervation caused wholesale changes in cytoskeletal organization that could be restored to normal by electrical muscle stimulation or external application of muscle agrin (Bezakova & Lømo 2001). These findings lead to new ideas about the function of muscle agrin, so far unknown, and how muscle activity controls the cytoskeleton to allow muscle fibres to handle the mechanical forces they generate or become exposed to.

The interest and activity created by the discovery of LTP has been amazing. I have been lucky to have played a small part and to live at a time where the opportunities for discovering new land in biology appear boundless.

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GLOSSARY

LTP: long-term potentiation
PTP: post-tetanic potentiation