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A prelude to long-term potentiation

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Searching for premonitory studies of hippocampal long-term potentiation (LTP), there is a paucity of data. While synaptic enhancement during repetitive activation was studied in several reports from many groups between 1955 and 1967, the reported after-effects were short, at the most lasting a few minutes. Responses lasting for more than 1 hour were not reported until 1973.

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1. A PROMISING CANDIDATE

LTP is a highly popular topic in neuroscience research. The great interest is generated by its properties, making it a useful candidate for cellular processes supporting learning behaviour. From the outset of this research in the 1960s, the most interesting features were the enhanced synaptic efficiency and the long duration. Later discoveries were even more important, namely showing cooperativity between activated afferent fibres and associativity, meaning respectively that synaptic enhancement requires coactivation of a certain number of fibres, and that an efficient synaptic input leads to the improvement of a weaker input, provided it is activated in concert with the stronger one.

After two preliminary reports (Lømo 1966; Bliss & Lømo 1970), the LTP saga was initiated in earnest by two well-known reports in *The Journal of Physiology* in 1973 (Bliss & Gardner-Medwin 1973; Bliss & Lømo 1973). In many fields of science, a major advance is often preceded by a distinct period of ferment in which the ideas of several people gradually develop, often in a competitive interchange between several scientists. When a perceived advance is made, it is often triggered by a new approach or an improved technique. Were there such premonitions before the LTP discovery? In my view, there was surprisingly little such gradual build-up in the field of hippocampal synaptic plasticity. Nevertheless, it may be of interest to examine some of the efforts to provide examples of simple cellular models for learning that circulated among neurophysiologists and which, to some extent, may have influenced the LTP discovery.

2. CLASSES OF MODELS

For more than 100 years, neuroscientists have been interested in the relation between nerve cells and their connectivity on one hand and cognitive abilities on the other. In an influential review, Kandel & Spencer (1968) distinguished between neural concomitants of learning (where the experimenter uses near-physiological inputs and outputs) and neural analogues of learning (results acquired with greatly simplified preparations). Did such ideas influence the scientists who were working in this field before 1973? To me, the answer seems obvious.

With its peculiar histological arrangement and high amplitude sinusoidal electroencephalographic signature (Jung & Kornmüller 1938), the hippocampus was seen as an interesting substrate for a search for basic cellular and synaptic analogues of learning. In particular, neuroscientists were looking for examples of long-lasting increases in synaptic transmission. Attempts to relate such activity to clinical memory studies came considerably later.

3. FACILITATED SYNAPTIC TRANSMISSION

Activity-dependent changes of synaptic responses come in several forms. These appear to be common to virtually all excitatory synapses, and have been particularly well studied by Magleby & Zengel (1975, 1976, 1982). After a single synaptic activation, excitatory synapses remain in a state that allows the synapse to release more transmitter for a period, peaking at *ca*. 10–20 ms and lasting for a few hundred milliseconds, a process called facilitation (Feng 1941). When the synapse is activated repeatedly, there is a marked enhancement of synaptic responses during, and for a few seconds after, the stimulating tetanus, a process Magleby called augmentation. Following a period of sufficiently high-frequency synaptic stimulation, the system remains in a state with increased transmitter release for several minutes, called post-tetanic potentiation (Feng 1941). Finally, at many excitatory synapses, perhaps mostly in the cortical tissue, a period of high-frequency synaptic activation is followed by an increased synaptic transmission efficiency, LTP. In the first analysis of this phenomenon, an event of 30 years ago, which is the reason for the present set of articles, Bliss & Lømo (1973) called the phenomenon long-lasting potentiation. A few years later, Douglas & Goddard (1975) proposed the name long-term potentiation, which has been generally accepted, perhaps because of its easily pronounced acronym. While both facilitation (Katz & Miledi 1968), augmentation and PTP

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

(Magleby & Zengel 1982) are due to presynaptic increased calcium levels after the activation, LTP is probably more complex, employing a set of both pre- and postsynaptic processes each with a different time profile. First, during the first 20–40 min, there is a gradual decline of response amplitude, called short-term potentiation, followed by a seemingly steady state, the LTP proper. The latter is split into two parts, an early, *ca*. 3 h long form and a later process, many hours long, the latter requiring new protein synthesis.

4. POST-TETANIC POTENTIATION AS A CANDIDATE FOR LEARNING PROCESSES

Lloyd (1949) reported that PTP of monosynaptic spinal reflexes could last up to 7 min. Eccles (1953) proposed that spinal cord synapses could be 'capable of "learning" to operate more effectively' through PTP, in particular if they were in a disused state before the activation. Spencer & Wigdor (1965) and Beswick & Conroy (1965) both reported PTP durations in spinal reflex pathways lasting for several hours, but the tetanizing frequency and duration were far outside the range normally encountered. In a thalamo-cortical-bulbar pathway, Amassian & Weiner (1966) observed much larger PTP mediated through cortical involvement than at spinal levels, but the duration was only 2.5 min. PTP is present in all hippocampal synapses tested, but it does not last for more than *ca*. 5 min after tetani of 100 Hz lasting for a few seconds.

In conclusion, in order to play a part in physiological mechanisms of learning, PTP is too short lasting to be a serious candidate.

5. FEEBLE PREMONITIONS OF THE LTP PHENOMENON

Were there any premonitions for the LTP discovery? The unusually large amplitude and synchronous appearance of the theta activity made several researchers feel that this transitory state might be correlated to a change in the state of the participating synapses. Several groups, therefore, studied the hippocampus, first with electroencephalographic techniques, later by recording signals evoked by stimulation of various afferent stations. Thus, Green & Arduini (1954) reported that the large theta waves were associated with phasic discharges of single hippocampal neurons. Green & Adey (1956) also recorded theta waves and felt they were changing in amplitude during learning. However, the relation between the large synchronous theta waves and the hippocampal function was difficult to analyse.

6. AUGMENTATION RESPONSES

By contrast, the tremendously enhanced signals observed during periods of repetitive stimulation impressed researchers as a case of plasticity not easily matched by other nervous regions. In particular, many research groups were impressed by the augmentation process occurring during repetitive stimulation of afferent fibres to hippocampal neurons. The first to report this phenomenon were Cragg & Hamlyn (1955) who noted the strongly enhanced responses of CA1 neurons in anaesthetized rabbits to stimulation of stratum radiatum fibres at 5–30 Hz. They used the term facilitation for the phenomenon. They were also the first to distinguish between the presynaptic volley and the subsequent postsynaptic wave (fEPSP) and reported that the postsynaptic wave was the only wave to potentiate during the repetitive activation. Significantly, they did not report any activity to outlast the tetanic stimulation.

In a paper 2 years later Cragg & Hamlyn (1957) again reported on prominent augmentation effects and surmised that 'The facilitation at low repetition rates may well be a property peculiar to large interconnected assemblies of neurons'. However, they did not report any effects after the tetanic stimulation.

7. EFFECTS FOLLOWING THE AUGMENTATION

Several other groups subsequently noted remarkable augmentation in many dentate or hippocampal synapses. A number of these authors also found that the enhanced synaptic responses outlasted the tetanic period. Green & Adey (1956) noted that 'prolonged bursts would sometimes potentiate for several minutes', while Gloor *et al.* (1964) reported after-effects but only for a few seconds. Andersen (1960*a*,*b*) also observed the augmentation, which he called frequency potentiation, during the tetanization. Following the tetani there were enhanced synaptic responses for 6 min in both the Schaffer collateral/CA1 synapses and commissural/CA3 synapses. In the septo-hippocampal system, the post-augmentation potentiation lasted up to 3 min (Andersen *et al.* 1961). By contrast, following entorhinal activation of dentate granule cells, the post-augmentation potentiated state only lasted 30 s, possibly because of the barbiturate anaesthesia used (Andersen *et al.* 1966). In their pioneering work on prepiriform cortical slices, Yamamoto & McIlwain (1966) reported that stimulation of the olfactory tract at 100 Hz for 10 s was followed by enhanced N-waves (fEPSPs) for 0.5–3 min, interpreted as PTP.

All of these groups were aware of the possible significance of the reported phase with enhanced synaptic responses following a period with intense activation. However, we all felt that the duration was not sufficiently long for these post-augmentation changes by themselves to form a realistic mechanism for learning changes. However, in cooperation with other processes they could be thought to play a part. For example, Andersen & Lømo (1967; report from a symposium in 1965) characterized the progressively slower decay of post-augmentation potentiated CA1 responses to commissural stimulation: 'an example of a primitive synaptic learning'. Later, they proposed 'It appears, therefore, likely that the frequency potentiation (=augmentation) of cortical synaptic activity may be a factor involved in the establishment of neuronal circuits of synaptic facilitated synaptic transfer as one might envisage happening during a learning process'.

8. LTP WAS A NEW ACTOR ON THE SCENE

The meagre data on durable changes of hippocampal synaptic responses reported before 1966 are reflected in Bliss & Lømo (1973), which only refers to the early

preliminary abstract by Lømo (1966). There is no reference to other authors using repetitive stimulation. There were two new aspects to their approach: first, the much longer duration of the post-tetanus synaptic enhancement and, second, their use of two divisions of the perforant path, a control pathway distributed to a virgin territory of the dentate gyrus next to the tetanized pathway. Thus, they could link the synaptic changes to the tetanized input and, later, show that the control synapses were, indeed, also able to undergo LTP changes. Finally, Bliss and Lømo clearly set the LTP phenomenon in relation to learning processes. Referring to Douglas (1967) and Olds (1972) who both reviewed hippocampal involvement in memory, they state 'synapses … influenced by activity which may have occurred several hours previously … a time scale long enough to be potentially useful for information storage'. The prelude was over, the concert had started.

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GLOSSARY

fEPSP: field excitatory postsynaptic potential
LTP: long-term potentiation
PTP: post-tetanic potentiation