6 Summary

Elucidation of the physiological mechanisms underlying learning and memory remains perhaps one of the greatest challenges facing the neuroscience community today. One of the significant advances in the past two decades in terms of advanced understanding of learning and memory, is the discovery and elaboration of a phenomenon called long-term potentiation (LTP), a long-term increase in synaptic efficacy that presumably represent neural correlates of learning in intact animal. The idea that seizure activity may induce LTP leads to a possible explanation for the phenomenon of kindling. Repeated alcohol intoxication and withdrawal also induces "epileptic kindling", a form of synaptic plasticity leading to seizures. This so-called kindling of convulsant activity has been suggested to reflect changes in efficiency of nervous transmission in the amygdala. The amygdala is crucially implicated in the formation of associations between discrete environmental events and aversive stimuli, and the expression of fear reactions governing behavioural, autonomic and endocrine responses to threat. The aim of the present study was the comparison of changes in basal transmission, short term plasticity (paired pulse facilitation) and long-term plasticity (LTP, long-term depression (LTD)) in the lateral nucleus of the amygdala of different animal models of temporal lobe epilepsy (amygdala kindling and pilocarpine treatment in Wistar rats) and alcohol withdrawal in Lister-hooded rats. The observation made in the present study in un-treated Wistar and Lister-hooded rats that the magnitude of LTP in the right lateral amygdala exceeds that in the left lateral amygdala is in line with findings of hemispheric lateralization of transmitter systems, and may provide a further link between long-term synaptic plasticity in the amygdala associated with the formation of Pavlovian fear memory and the lateralization of these functions.

Wistar rats were kindled through daily administration of brief electrical stimulations to the left basolateral nucleus of the amygdala, and resulting motor seizures were scored according to the Racine scale. Field EPSPs (extracellular recordings) or EPSPs (intracellular recordings) were recorded in the lateral nucleus of the amygdala in horizontal slices derived from kindled rats 48 hours after the last induced seizure, and in slices from sham-implanted and non-implanted controls. We could show that kindling produced some general saturation of potentiation since 48 h after the last kindling-

induced seizures LTP in the lateral nucleus of the amygdala was significantly reduced, the magnitude of which was dependent on the number of prior stage V seizures. A similar depression of LTP was also obtained in pilocarpine-treated animals which developed spontaneous seizures before the *in-vitro* experiments as well as in rats which have undergone single or repeated alcohol withdrawal. This depression of LTP may be the electrophysiological basis for memory disturbances observed in animals after kindling or in patients with temporal lobe epilepsy and after alcohol withdrawal, respectively. In the same rats, in which we have done our electrophysiological experiments these repeated episodes of high alcohol consumption and withdrawal impaired the ability to form conditioned associations between discrete stimuli and aversive unconditioned stimuli. The apparent paradox of heightened seizure sensitivity, and exaggerated anxiety responses during withdrawal, but impaired fear conditioning, could then be accounted for if repeated experience of withdrawal induces synaptic plasticity, resulting in facilitated transmission, but reduced capacity for further plasticity necessary for learning. Whereas in amygdala-kindled rats the excitability was increased in the amygdala, paired pulse facilitation was not influenced by the different treatments and most of the cell parameters of pyramidal-like neurons were unchanged in comparison to controls. Interestingly, stimulus paradigms which induced in non-implanted and sham-implanted controls long-term depression of synaptic activity (theta pulse induced LTD or low frequency stimulation-induced LTD), caused LTP in kindled rats. Thus, the induction of LTP in kindled rats by usually LTD-inducing stimulation parameters may be the result of a kindling-induced threshold change. In more general terms, changes in transmitter function in the treated animals might alter the optimal physiological conditions for induction of LTP or LTD, they could disrupt the strength, pattern, or effectiveness of plastic changes related to learning. According to this hypothesis, then, kindling may represent an enduring form of metaplasticity, which results in a shift away from the optimal “settings” for learning.

To get a better insight in functional reasons of pathological neuroplasticity in kindled animals, we partially blocked the GABAergic transmission or tried to enhance the glutamatergic transmission. Partial blockade of GABAergic transmission with the specific $GABA_A$ receptor antagonist, SR 95531 (0.1 µM), significantly facilitated the induction of LTP extracellularly recorded in all animal groups, but did not abolish the kindling-induced impairment of LTP completely. In contrast, the specific kainate GluR5 agonist, ATPA (2 µM) caused a weaker LTP in age-matched controls.

However, it enhanced the magnitude of LTP (intracellularly and extracellularly recorded) in kindled animals, which reached 7 times stage V seizures in such a way that LTP in ATPA-treated slices did not significantly differ from that recorded in drugfree, non-implanted controls. Therefore, the stimulation of kainate GluR5 receptors can compensate for the kindling-induced plasticity changes in the amygdala. However, ATPA did not influence LTP in pilocarpine-treated animals. In summary, continued growth in our understanding of the diverse consequences of kindling induced by different paradigms and their dynamics should also help identify which candidate mechanisms of memory function may be affected by seizures.