Synaptic plasticity dysfunction *in vivo*

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Persistent activity-dependent increases and decreases in synaptic transmission provide an attractive biologically plausible means of information storage in the brain. Since different types of stress can facilitate or impair memory great interest has focused on how stress affects synaptic plasticity. Dysregulation of the induction or maintenance of hippocampal synaptic plasticity may be of importance in stress-related psychiatric disorders such as depression where normal hippocampal function is often impaired [1].

Exposure to a novel inescapable environment that causes behavioural freezing blocks the induction of long-term potentiation (LTP) of excitatory transmission in the rat hippocampus (CA1 area) [2-5]. It also can facilitate long-term depression (LTD) [2, 3]. The stress-induced switch in the direction of plasticity was found to be dependent on corticosteroid action at glucocorticoid receptors, and is regulated by drugs that alter brain 5-HT at least partly via 5-HT2 receptors. In contrast, exposure to a novel non-stressful inescapable environment that causes active exploration triggers a rapid reversal of previously established LTP within a defined time window but also facilitates new LTP induction in a different time window [6, 7].

Somewhat similar to the effects of inescapable stress, we have discovered that hippocampal LTP is inhibited by the Alzheimer disease-related peptide amyloid ß (Aß) in vivo after intracerebroventricular injection [8-12]. Moreover Aß also promotes LTD in vivo [13]. Such disruption of plasticity mechanisms is mediated by small abnormally folded oligomers of Aß via pro-inflammatory/ oxidative and nitrosative stress mechanisms and is dependent on many neurotransmitter receptors / signaling pathways and integrins [14].

Here we present recent data comparing the effects of treatments that disrupt synaptic plasticity in vivo either in awake, freely behaving animals or under anaesthesia. Briefly, Male Wistar rats are housed under a twelve h light-dark cycle. Prior to surgery animals were anaesthetised with urethane (ethyl carbamate; 2.1g/kg, i.p.) for non-recovery experiments or a variety of anaesthetics for recovery experiments. Monopolar recording electrodes and bipolar stimulating electrodes are made in the laboratory from two lengths of Teflon coated tungsten wire. A stereotaxic apparatus is used to place the electrodes in the CA1 area of the dorsal hippocampus. Electrophysiological criteria are used to determine the optimal electrode placement. Field excitatory post-synaptic potentials (fEPSPs) are recorded from the stratum radiatum following stimulation of the Schaffer collateral-commisural pathway. Test fEPSPs are evoked by a single square wave pulse of current at low frequency (0.033Hz). The test stimuli evoked responses of between 50-55% maximum fEPSP amplitude. The high frequency stimulation (HFS) protocol to induce LTP comprises trains of pulses at different frequencies (100-400Hz). For recovery experiments animals are habituated to the recording box and at least one week is allowed for recovery from surgery.

We have discovered many different effects of the different treatments on baseline synaptic efficacy and synaptic plasticity, depending on experimental protocol and behavioural conditions. The presentation will outline some of these experimental variables.

The ability of stress to dramatically alter the induction of different types of synaptic plasticity in the hippocampus is believed to play a key role in mediating the effects of stress on hippocampus-dependent memory and learning. Increasing our understanding of the contributions of behavioural factors and cellular mechanisms should greatly aid the development of new approaches to stress-related cognitive disorders.

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