Investigation of structural and functional properties of ex-vivo human epileptic hippocampus

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Investigations of rat cerebral cortex neurons growing in tissue culture indicate that during brain development, homeostatic mechanisms operate, which keep the levels of spontaneous electrical activity within physiological limits. When spontaneous electric activity in cultured neuronal networks is blocked for a prolonged period and then allowed to return, the pattern of activity has changed dramatically, showing a considerable increase in stereotyped burst firing. This stereotyped burst firing can be replicated by partial suppression of GABA-A-mediated inhibition. It therefore appears that prolonged suppression of electric activity in developing networks promotes excitatory drive by increasing the ratio between excitatory and inhibitory network formation. Subsequent studies have revealed a negative feedback loop whereby activity-dependent release of BDNF preferentially stimulates GABAergic neurotransmitter system development, resulting in a net decrease in overall network activity. Disregulation of this homeostatic feedback loop during human brain development could result in an imbalance between excitation and inhibition and result in an increased susceptibility to generate epileptic seizures.
To investigate this hypothesis, we are accumulating both fixed and frozen hippocampal and cortical tissues derived from epileptic patients undergoing surgery for intractable epilepsy and from non-epileptic post-mortem brains with minimal post-mortem delays. These tissues are examined for properties of the excitatory and inhibitory neurotransmitter systems and levels of neurotrophins and their receptors, using histological and biochemical methods. Functional aspects of the epileptic circuitry can be measured by recording electric activity from ex-vivo cortical/hippocampal slices cultured on top of multi-electrode arrays with 60 microelectrodes. Culturing of the ex-vivo (epileptic) tissue moreover enables experimental manipulation and analysis of the effects of neurotrophins, electric activity and anti-epileptic agents on the physiology and connectivity of the cultured slices.
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