# NEURAL MECHANISMS OF ANAESTHESIA

Ahmad Hashemi-Sakhtsari

Thesis submitted for the degree of

Doctor of Philosophy

in

Faculty of Science

The University of Adelaide

Department of Physiology December 1994

CONTENTS

# ABSTRACT

Despite almost a century of research, the mechanisms of anaesthesia remains obscure. Stereoselectivity of anaesthetic agents supports interaction of anaesthetic agents with cellular protein targets rather than an indiscriminate perturbation of the lipid bilayer as was previously proposed. In general, at neural level anaesthesia is produced by reducing excitation or enhancing inhibition. In the 1990s, the hypothesis that anaesthetics in large part produce their pharmacological actions at specific loci on the $GABA_A$-receptor complex has become most favoured. In this thesis, possible neural mechanisms of action of general Anaesthesia are introduced.

Preliminary evoked potential recordings from the brain of anaesthetised rabbits are presented, before proceeding to report *in vitro* studies of a slice preparation from rat brain using a grease-gap recording model which allows detailed investigations in a relatively undisturbed, but controlled environment. Cellular excitatory mechanisms leading to spontaneous epileptiform discharges in the neocortical slices in a $Mg^{2+}$-free artificial cerebro-spinal medium are discussed.

Potassium channels control cell excitability and its firing properties. The study of effects of various classical potassium channel blockers on spontaneous discharges from neocortical slices has revealed that, as well as causing tissue excitability, each agent has definite signatory effects on individual discharges. Modern spectral analysis of the

after-activity of responses enabled numerical values for frequency and power density of control, and discharges in the presence of each potassium channel blocker to be obtained.

4-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system, its actions being mediated through both $GABA_A$- and $GABA_B$-receptors. The effects of $GABA_A$- and $GABA_B$-receptor agonists and antagonists on spontaneous discharges in the slice model are presented and discussed. These studies suggest that agents acting on GABA receptors can intensely modulate neuronal activity, providing a conceivable basis for the actions of both analgesic and anaesthetic agents.

Finally interaction studies between baclofen, a $GABA_B$-receptor agonist, and various potassium channel blockers identifies baclofen as a potent agent in diminishing or abolishing spontaneous discharges. These studies show that, with the exception of $Ba^{2+}$, baclofen is capable of suppressing the hyperexcitability induced by potassium channel blockers.