A. Introduction

Antiepileptic drugs have been the mainstays of the treatment of patients with epilepsy. From 1978 to 1993 the primarily used antiepileptic drugs have been phenytoin, carbamazepine, barbiturates and primidone, benzodiazepines, valproic acid and ethosuximide. Recently a number of new antiepileptic drugs have been developed which include gabapentin, lamotrigine, oxcarbazepine, vigabatrin, tiagabine, topiramate and felbamate. Unfortunately, early experience with felbamate was associated with an unacceptably high incidence of aplastic anaemia (PENNELL et al. 1995) and chemical hepatitis, and in August of 1994 the manufacturer and the United States Federal Drug Administration recommended that, if clinically possible, patients be withdrawn from felbamate. Fortunately, the remaining newly developed antiepileptic drugs have been approved in many countries and are currently in use.

Interactions of the established and new antiepileptic drugs with neurotransmitter receptors or ion channels may be responsible for their clinical effects (MACDONALD and KELLY 1994; MACDONALD and MELDRUM 1995; MACDONALD and GREENFIELD 1997). Three primary neurotransmitter receptor or ion channels are targeted by the established antiepileptic drugs and by some of the newly developed antiepileptic drugs: γ-aminobutyric acid type A (GABA_A) receptor channels, voltage-dependent Na⁺ channels and voltage-dependent low threshold (T-type) Ca²⁺ channels. The actions of the established and recently developed antiepileptic drugs on specific neurotransmitter receptors or ion channels will be reviewed.

B. Established Antiepileptic Drug Mechanisms of Action

I. Phenytoin and Carbamazepine

Phenytoin and carbamazepine have been shown to interact with voltage-dependent Na⁺ channels at concentrations found free in plasma in patients being treated for epilepsy (MACDONALD 1989 and Table 1). These drugs were demonstrated to reduce the frequency of sustained repetitive firing of neurons. A property of these drugs was that they did not reduce the amplitude or duration of single action potentials but reduced the ability of neurons to fire trains
of action potentials at high frequency. The limitation of high frequency repetitive firing was voltage-dependent, with limitation of firing being increased following depolarization and reduced following hyperpolarization. Once developed, the limitation of firing was prolonged, lasting several hundred milliseconds. The action of the antiepileptic drugs appeared to be due to a shift of Na⁺ channels to an inactive state from which recovery was delayed.

Both phenytoin and carbamazepine produced a voltage-dependent block of mammalian myelinated nerve fibre Na⁺ channels that could be removed by hyperpolarization, a shift of the steady-state Na⁺ channel inactivation curve to more negative voltages and a reduction in the rate of recovery of Na⁺ channels from inactivation (SCHWARZ and GRIGAT 1989). Sodium channels recovered from complete inactivation in a few milliseconds following a 500-ms depolarization to 25 mV. In the presence of 100 µM phenytoin or carbamazepine, however, recovery was prolonged to 90 or 40 ms, respectively. Phenytoin and carbamazepine (50 µM) each produced a frequency-dependent block. However, the frequency-dependent block produced by carbamazepine was somewhat less pronounced than that produced by phenytoin. Thus, phenytoin and carbamazepine produced voltage-dependent and frequency-dependent block of Na⁺ channels. Of interest was the finding that phenytoin had a longer time-dependence for frequency-dependent block and for recovery from block than carbamazepine. This would result in more a pronounced frequency-dependent block for phenytoin than for carbamazepine. Thus, although phenytoin and carbamazepine have qualitatively similar actions on Na⁺ channels, the actions are quantitatively somewhat different. This may explain, at least in part, differences in efficacy for these two drugs in different patients.

Phenytoin had similar effects on human Na⁺ channels (TOMASELLI et al. 1989). Total mRNA was extracted from human brain and injected into Xenopus oocytes. The human brain Na⁺ channels expressed in oocytes were also blocked by phenytoin in a voltage-, frequency-, and time-dependent fashion. On rat hippocampal neuron Na⁺ currents, phenytoin (200 µM) produced a 20 mV negative shift in the steady-state inactivation curve and a frequency-dependent block of Na⁺ channels (WAKAMORI et al. 1989; KUO and BEAN 1994). Frequency-dependent block was shown at frequencies as low as