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Voltage-dependent sodium channels and excitatory amino acids

Introduction

Thromboembolic stroke causes the death of neurons by depriving the brain of an adequate supply of oxygenated blood. This process is termed cerebral ischaemia and is primarily a vascular event which leads to the damage of brain tissue and impaired function. Stroke is the third leading cause of death after coronary heart disease and cancer, and is an important source of adult disability in Europe and the United States (Bonita, 1992).

The existence of cerebrovascular disease has been recognized for centuries. Indeed, the ancient Greeks were the first to identify and misunderstand stroke. Hippocrates, the father of modern medicine, wrote as long ago as 400 B.C. that "unaccustomed attacks of numbness and anaesthesia are signs of impending apoplexy" (Fields and Lemak, 1989). However, the ancient Greeks lived in a world which they poorly understood, and they believed that they were at the mercy of nature. They considered stroke to be a random, uncontrollable event. And many of Hippocrates' aphorisms form the basis of modern concepts of stroke. For instance, we derive our modern word for stroke, apoplexy, from the ancient Greek word *plesso* meaning "to be struck with violence" or "to be thunderstruck". These misperceptions continued well into the late 17th century because stroke was believed to be a divine judgement. Interestingly, the *Oxford English Dictionary* of 1599 defined apoplexy as "a stroke of God's hands".

These misunderstandings persist even today. They are based on the assumption that there is little that a physician can do to ameliorate the consequences of a stroke except perhaps stabilize the patient and treat the complications. Furthermore, many people dismiss stroke as a natural consequence of growing old. Despite several setbacks, however, recent experimental developments are changing these ideas.

Cerebral ischaemia triggers a chain reaction of electrical and chemical activity encompassing ischaemic depolarization, excessive release of glutamate and increases in intracellular Ca^{2+}. These events act in concert to orchestrate cell death. Current neuroprotective strategies concentrate on interfering with one or more of these processes. Although glutamate antagonists selective for the N-methyl-D-aspartate (NMDA) receptor-channel complex have attracted a lot of attention, they have a very narrow therapeutic index which may limit their clinical usefulness. Consequently, many researchers have focused their efforts on studying the role of voltage-dependent Na^+ channels in cerebral ischaemia. And a considerable amount of progress has been made in this area recently. The aim of this section is to present some of the latest

preclinical research into how voltage-dependent Na^+ channels interact with excitatory amino acids to elicit neuronal death during ischaemia. Furthermore, we shall also describe the impact of some of the latest clinical developments on current thinking in stroke research.

Tiho Obrenovitch and Jutta Urenjak (1998) argue against the notion that blockers of voltage-dependent Na^+ channels may be neuroprotective primarily because they inhibit presynaptic glutamate release. And they complement this notion by proposing that these compounds protect neurons by reducing their energy demand and preserving the inward Na^+ gradient, upon which vital ion exchange and transport processes depend (Urenjak and Obrenovitch, 1998). Finally, I describe some of the problems associated with the use of current neurprotective agents such as NMDA receptor antagonists and blockers of voltage-dependent Na^+ channels for the treatment thromboembolic stroke (Carter, 1998). And I also suggest how these difficulties may be overcome by designing better blockers of voltage-dependent Na^+ channels.

References

Bonita R (1992) Epidemiology of stroke. Lancet 339: 342–344

Carter AJ (1998) The importance of voltage-dependent Na^+ channels in cerebral ischaemia. Amino Acids 14: 159–169

Fields WS, Lemak NA (1989) A history of stroke. Oxford University Press, New York

Urenjak J, Obrenovitch TP (1998) Neuroprotection-rationale for pharmacological modulation of Na^+ channels. Amino Acids 14: 151–158

Obrenovitch TP, Urenjak J (1998) Glutamate release inhibitors: a critical assessement of their action mechanisms. Amino Acids 14: 143–150

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