CHAPTER 9

Virus-coded Ion Channels as Antiviral Targets

STEPHEN GRIFFIN

Leeds Institute of Molecular Medicine, Faculty of Medicine and Health, University of Leeds, Wellcome Trust Brenner Building, St. James' University Hospital, Beckett Street, Leeds LS9 7TF, UK
Email: s.d.c.griffin@leeds.ac.uk

9.1 Introduction

Since the 1960s, it has been known that the adamantane drugs amantadine (1-adamantylamine) and rimantadine [1-(1-adamantyl)ethanamine] (see Table 9.2) exerted an antiviral effect against the entry of influenza A viruses, which led to them being one of the first antiviral prophylactic treatments licensed for use in humans. However, it was not until the 1980s that the molecular target of adamantanes was revealed by resistance mapping to be the M2 protein, a minor component of the infectious virion. M2 was subsequently shown to form a tetrameric proton channel, acting to mediate acidification of the virion interior and so promote efficient uncoating of the viral nucleoprotein. Today, despite a precise understanding of the M2 channel atomic structure, its key functional determinants and its role during the influenza life cycle, amantadine and rimantadine remain the only licensed antivirals targeting the M2 ion channel, and their clinical use is heavily restricted by resistant viral variants which now populate the majority of circulating isolates. It is hard to recollect another example of a class of antivirals where such initial progress has not been further capitalised upon up to the present day, leaving the therapeutic potential of an essential drug target untapped.

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