Mechanism of Inhibition of Viral and Neuronal Pore Loop Ion Channels by the Adamantanes

https://neurodegenerationresearch.eu/survey/title-of-pimechanism-of-inhibition-of-viral-and-neuronal-pore-loop-ion-channels-by-the-adamantanes/

Title of project or programme

Title of PI	Mechanism of Inhibition of Viral and Neuronal Pore Loop Ion Channels by the Adamantanes

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
Dr	Jason	Schnell	University of Oxford	UK

Address of institution of lead PI

Institution	University of Oxford
Street Address	South Parks Road
City	Oxford
Postcode	OX1 3QU

Country

- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

580086.05

Start date of award

20-08-2010

Total duration of award in months

36

The project/programme is most relevant to

- Alzheimer’s disease and other dementias
- Parkinson’s disease

Keywords

Research abstract in English

Adamantane-based drugs inhibit a wide range of ion channels with different structures and ion selectivities. Historically, they have been used to treat influenza infections because they inhibit the

virus M2 proton channel. The spread of resistant virus has, however, rendered the adamantanes essentially useless. Recent experiments in this lab have suggested that the M2 adamantane binding site is composed of functionally important, and therefore highly conserved, residues; there is therefore the possibility that alternative antiviral drugs could be found by targeting this conserved pocket. Thus, Part A of this proposal is aimed at determining the components of M2 that are critical for drug binding, with the ultimate goal of informing the design of next generation antivirals. Adamantanes are also used for the treatment of dementia associated with Alzheimers and Parkinsons diseases. The therapeutic target for this indication is the ion channel domain of the ionotropic NMDA receptor. Although, high-resolution structures of the intact ionotropic NMDA receptor have not been determined due to its size and complexity, the viral ion channel Kcv is a structurally homologous pore-loop ion channel that is also inhibited by the adamantane amantadine. Thus, Kcv is a useful surrogate for studies that focus on adamantane binding and inhibition of this class of ion channels. In Part B and C of the proposal, we will use techniques developed for the investigation of adamantane binding to M2 to establish and exploit an experimental system for the study of adamantane binding to Kcv at the atomic level, and by extension, to the NMDA receptor ion channel. Functional studies using liposomal ion fluxes will validate and extend the structural work. It is anticipated that a detailed characterization of the position and structural and dynamic effects of drug binding within the context of these disparate ion channel structures will provide information for new approaches to drug design for this class of valuable ion channel inhibitors.

Lay summary
In which category does this research fall?

- Basic research