Development of novel small-size peptides as putative therapeutic drugs

Masman, Marcelo Fabricio

Summary

Development of Novel Small-Size Peptides as Putative Therapeutic Drugs

Rational design of peptide drugs using computational techniques. This thesis focuses on the development of small peptide molecules with putative therapeutic applications. In particular, our research has been focused on peptides with either antifungal properties (chapters 2-4) or with the ability to control protein deposits that cause the characteristic brain damage in Alzheimer's disease (chapters 5-7). In modern medicinal chemistry research, the use of computational techniques has become an important and almost inevitable step towards the development of new drugs. With these techniques it is possible, with certain accuracy, to simulate what happens between a newly developed drug and its target molecule(s), e.g. protein, DNA, cell-membranes, etc. Molecular dynamics is one of the computational techniques used in this thesis, and perhaps the one most frequently applied in modern medicinal chemistry. Based on the results of these types of calculations, new potential drugs were designed to achieve the optimum desired effects.

New Peptide Drugs for the treatment of fungal infections. Fungal infections in humans are common and may affect skin, intestines, heart, and brain, amongst other organs. Fungi are difficult to combat and can be life threatening, especially in AIDS patients, cancer patients after chemotherapy, organ transplanted patients, diabetes, burns, malnutrition, etc. This is due to the fact that their immune system is remarkably weak, creating an ideal situation for fungi to attack. Fungal infections are difficult to suppress and a really selective, safe and effective drug to treat this type of infections is not yet available. Thus, there is a great need of producing innovative and selective antifungal drugs. Small peptides derived from naturally occurring compounds have been taking under study in this thesis. The antifungal activities of these peptides have been tested in culture for several common pathogenic fungi. These antifungal peptides showed a promising profile to become a selective drug that might exert their effect through interaction with the cell-membrane of the fungal cells.

Novel peptides to protect against Alzheimer's Disease. Alzheimer's disease is a very complex disease where brain damage is associated with an increased degradation of the human mind and memory. Multiple factors play a role in causing the disease, but researchers agree that the production of a specific toxic form of the beta-amyloid peptide plays a key role. This peptide is not toxic by itself but it becomes toxic when several beta-amyloid molecules clump together forming what is called soluble aggregates. In this form the beta-amyloid become

toxic to nerve cells and a slow but unstoppable degradation process begins in brain regions that are essential for learning and memory, which in the course of years leads to the characteristic dementia. The currently available drugs for treating Alzheimer's disease have little impact and may, at best, delay the loss of memory, but do not stop the degradation process of the nerve cells. The severity of the disease and the enormous increase in the number of patients suffering from it, are the driving force of a worldwide search for new and more effective drugs. In our own research we focus on the development of new peptide compounds that prevent or slow down the formation of the toxic beta-amyloid soluble aggregates. By the use of computational techniques, we have been able to explore the self-bound beta-amyloid molecules, as well as their interaction with new potential drugs. With this important information we have designed small peptide drugs aimed at disrupting the toxic form of amyloid. The anti-amyloid potential of these peptides has been tested, in the first place, by cultured brain cells which have been exposed to toxic beta-amyloid forms. Secondly, we have tested these anti-amyloid peptides in the 'hippocampus' of mouse brain, a typical brain area affected in the Alzheimer's patient and which is the key structure for the formation of memory. Both testing experiments have produced not only positive but promising results indicating the potential therapeutic application of these anti-amyloid peptides.▪