Abstract

Free fatty acid receptors 1 and 4 (FFA1, 4) are 7-transmembrane domain (7TMD) proteins, activated by medium and long chain fatty acids (MCFA, LCFA). Expressed in the pancreas and intestinal cells, their activation leads to beneficial glucose-lowering effects making them attractive targets against type-II diabetes. The receptors, however, are also expressed in the brain, especially in the hypothalamus, with their role there less extensively investigated. Recent studies revealed that hypothalamic FFA1 and FFA4 regulate energy homeostasis and inflammation whereas they also increase neuronal leptin sensitivity and promote hypothalamic neurogenesis. Multiple studies on animal models of diet-induced obesity have shown that FFAR activation in the hypothalamus leads to a reduction in energy efficiency, body mass weight and adipose tissue. Such findings highlight the potential of these receptors towards the treatment of obesity and related metabolic disorders.

Chapter 1 describes our effort to target these hypothalamic receptors using a prodrug approach. The recently discovered transporter MFSD2A, highly enriched in the blood brain barrier (BBB) endothelial cells (EC) shuttles fatty acids like docosahexaenoic acid (DHA) into the brain esterified as lysophosphatidyl cholines (e.g.: LPC-DHA). We thus designed molecules based on this scaffold bearing known FFA1 agonists. To this end we report the development of a regiospecific route which gives access to both natural and synthetic LPC-conjugates with late-stage introduction of fatty acids. The route was also employed towards the synthesis of stable isotope-labelled palmitoyl-LPC for the first time. Pharmacokinetic (PK) studies on this labelled LPC-conjugate validated the advantage of dosing the FFA1 agonist esterified as an LPC-conjugate compared to the administration of the FFA1 agonist alone. Further PK studies will elaborate on whether such observations hold true for the synthetic analogues described hererin.

Chapter 2 describes another approach towards targeting the FFA1 in the central nervous system (CNS). Namely, the design and synthesis of a small series of apolar compounds is described. *In silico* analysis indicates that such ligands can potentially cross the BBB. The analogues were tested *in vitro* and found to be partial agonists of the receptor. Further evaluation of the BBB penetration of such compounds will provide valuable information for future compound development.

In chapter 3 the health issue of cognitive decline in the elderly is addressed. The positive association between sphingomyelin (SM)-containing food products and cognitive enhancement has been suggested by multiple groups. In our efforts to establish a direct causal relationship between dietary SM intake and cognitive enhancement, we aimed at elucidating the bioavailability and biodistribution of SM after oral administration. To this end we designed and produced for the first time, a triple stable isotope-labelled SM molecule. Efforts to optimize the synthesis towards this SM tracer analogue are described herein. Serendipitously and contrary to expectation, we discovered that the route led to the formation of by-products as a result of alkene isomerization in the cross-olefin metathesis reaction. A mechanism for such by-product formation is postulated. Further optimization of the synthetic route is required to improve the route's scalability.

Chapter 4 covers the development of a protocol for the alkoxycarbonylation of (hetero)aryl bromides under mild reaction conditions.