Chapter 6

MRI tractography, neuroanatomical and clinical trial verification for hepatomodulatory drugs

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6. MRI tractography, neuroanatomical and clinical trial verification for hepatomodulatory drugs for Alzheimer's Disease therapy

Literature review, hypothesis and work plan:

Alzheimer's disease (AD) requires an alternative therapeutic perspective because newer approaches to AD using neurological drugs sometimes have suboptimal or lesser effect. It is now known that AD is actuated by amyloid accumulation rather than amyloid formation, and a main pathogenesis is due to reduction of amyloid elimination, which occurs primarily through the liver into bile and feces [11]. Hence, hepatomodulatory drugs that can enhance this hepatic clearance of amyloid may be a physiological therapeutic approach to AD. Animal studies show that such drugs can reduce brain amyloid and reverse behavioural-cognitive deficits of AD [138]. Hence, we may infer that these drugs might also have potentiality to alleviate human AD. We have earlier developed a robust systems biological approach to this aspect, showing that hepatic clearance of brain amyloid can be enhanced via three pathways: (a) Pregnane-X-receptor, (b) Bile salt export-pump receptor, (c) Phosphodiesterase inhibition, and that these pathways can be activated respectively by three candidate molecules: (i) Rifampicin, (ii) Metformin, (iii) Cilostazol [139] (Figure 35).

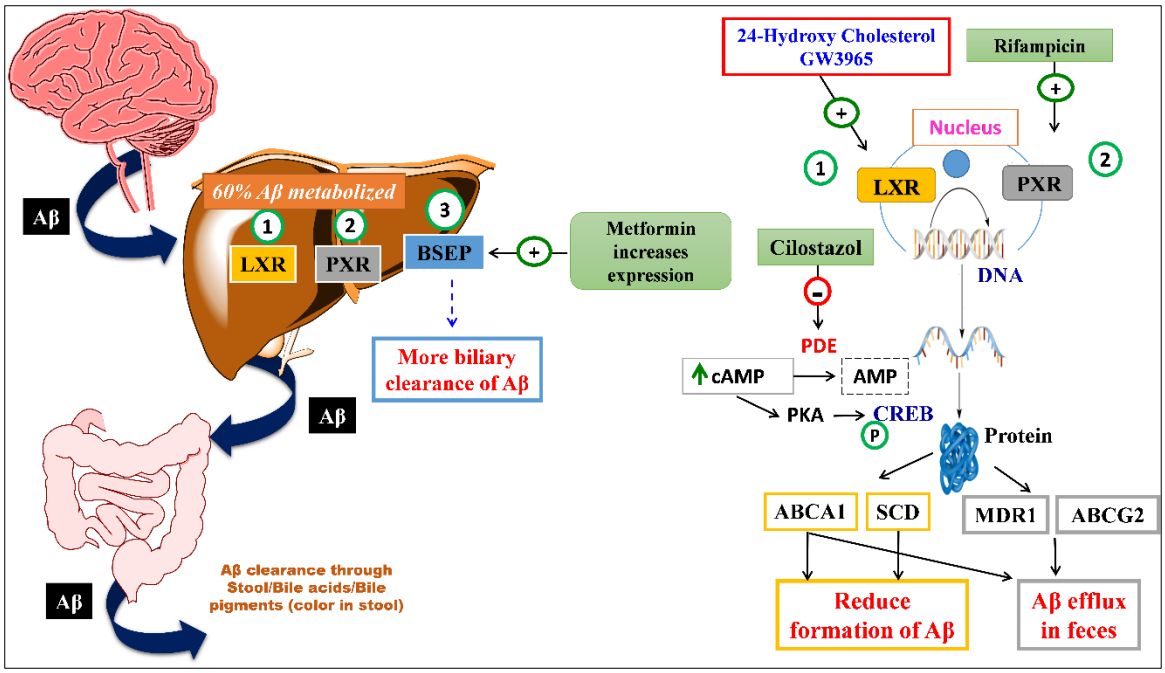

Figure 35: *Schema of the three pathways of the hepato-biliary-faecal elimination route of amyloid beta of brain, each pathway can be enhanced by a corresponding pharmacological agent.*

Furthermore, we have earlier developed a histologically-validated MRI-DTI approach showing that axonal white matter tracts may function as migration scaffold in human brain, e.g. transport of glioma cells and stem cells [140]. Hence, we can take that this MRI tract network can also be a scaffold for amyloid spread in brain, moreover so as rodent models show that amyloid and prion spread occurs along axons [141]. Our previous study discussed in Chapter 3 (Figure 21), revealed that the combination of rifampicin, cilostazol, and metformin was more synergistic than other combinations. Hence, in this chapter we are aiming to find the different neural regions activated by these drugs in AD patients to provide a deeper neuroanatomical rationale to their therapeutic efficacy.