

Chapter 4

Hepatometabolic agents as a therapeutic intervention in Alzheimer's disease

Chapter 4

4. Hepatometabolic agents as a therapeutic intervention in Alzheimer's disease

Literature review, hypothesis and work plan:

4.1 Hepatometabolic agents and Alzheimer's Disease

We approach Alzheimer's disease from a metabolic-metabolite angle, with a focus on the body's main metabolic platform, the hepatobiliary system. There are several etiopathogenesis mechanisms regarding Alzheimer's disease (AD), among which the amyloid beta (A β) hypothesis is more predominant. Indeed, most (about 70%) of A β is metabolized by the liver [11]. We provide attention to the basic hepatobiliary metabolite, as bile acid, where cholic acid is a primary constituent. Moreover, Li et al reported that Cholic acid significantly maintained the integrity of blood-brain barrier and mentioned that it can also be able to diffuse across phospholipid bilayers and further cross the blood-brain barrier [83]. Some steroidal substances, including certain neurosteroids, show neuroprotective behaviour, and these steroids and cholic acid are comparable molecules (cholesterol derivatives), whereby cholic acid can act as ligands for such nuclear receptors to enable neuroprotection [84]. Additionally, cholic acid can act as a neurotropic agent by diminishing neuroinflammation, decreasing oxidative stress, and by expressing neurotrophic factors [85].

Several reports suggest that hepatic dysfunction enhances amyloid level in brain as also incidence of Alzheimer's disease [86]. One also knows that that cholic acid can prevent amyloid deposition in Alzheimer models as rodents as they age with time [87]. Ageing causes change in liver morphology leading to hepatic dysfunction and reduction in bile acid synthesis in geriatric subjects [88]. Cholesterol metabolism is also affected by ageing, causing less CA secretion into the bile and interruption in enterohepatic circulation [89]. As a consequence of which, the brain acquires less CA, thereby the lower CA level in the blood could increase the A β burden in the brain.

The amyloid formed in the brain undergoes clearance by the blood, which is the main route of amyloid elimination from the brain, and it has been experimentally shown that this cerebral vascular clearance of amyloid decreases in AD [10]. Moreover, lower cerebral blood flow (CBF) is associated with faster cognitive decline [90] and lower CBF is a measure for early detection of AD [91]. Thus, we see that from a metabolic perspective, the main players in Alzheimer's disease can be cholic acid, amyloid-beta and cerebral vascular flow. Deciphering and understanding the causative relations between them is a main aim of our study.

4.2 Causation Analysis

Analysis of data in clinical neuroscience and neurology has largely been oriented on correlation and association of parameters. However, such analysis does not delineate cause-effect process, and thus it is difficult to develop cause-effect relationship between different parameters of the human pathophysiological system. Unless causation framework of the neuro-pathophysiological system is known, it is difficult to formulate therapeutic or interventional operations that could affect to pathophysiological causative factors, thus precluding any significance for future treatment aspects. In this study, we explore the possibility of delineating causative approach to the neurological milieu, with special attention to the scenario of the major contemporary neurodegenerative aspect with large global socio-economic hazard, namely, Alzheimer's disease and its sequelae disorder, Mixed Dementia.

As mentioned, we aim to elucidate in human subjects whether there are any cause-effect relationships causative relationship between cholic acid, amyloid beta load and cerebral flow, and the direction of the causations. Granger causality is a standard vector autoregressive methods initially proposed in statistical studies[92, 93]. The idea of Granger Causality is elementary and intuitive, where if temporally earlier (lagged) values of X help

predict current values of Y in a forecast formed from lagged values of both X and Y, then X is said to cause Y [94]. We have earlier used Granger causation analysis technique in fMRI data to estimate effective connectivity and causality direction between BOLD signals of brain areas [95]. In our study, we implement this approach by regressing amyloid-load signal (SUVR) on cholic acid level signal (CA) and on amyloid level signal (SUVR). If the coefficients of the time-consecutive (lagged) cholic acid signal are significant as a group, then it can be estimated that cholic acid parameter causatively alters and affects the amyloid load (SUVR), i.e., this estimation furnishes the strength of the causation in the direction:

Cholic acid → Amyloid load.

We assessed the aforesaid causation dynamics here. On the other hand, we also need to evaluate the possibility of reverse causation, i.e.

Amyloid load → Cholic Acid.

Moreover, we also further probed the causation process, incorporating the other variable, CBF. That is, we endeavoured to assess the causality relationship between amyloid load and CBF, as also the causative relationship between cholic acid and CBF.

4.5 Imaging Modalities

Imaging methodologies are now available for investigating these dynamics. Arterial spin labelling (ASL) is a non-invasive perfusion MRI that quantifies CBF utilizing electromagnetically labelled arterial blood water [96]. Moreover, Positron Emission Tomography (PET), an in vivo imaging technique with a specific radioactive tracer, can quantify A β load. The 18F-AV45 (florbetapir), a PET radio-tracer, can be uptaken in the cortical regions affected by AD, with more A β accumulation [97]. The Standard Uptake Value Ratio (SUVR) is used to quantify the amount of tissue uptake of PET tracers which gives a quantitative measure for A β load [98].

4.6 Framework of the investigation

Our present investigation aims also to study the alteration of cholic acid levels between healthy controls and AD subjects. Furthermore, we also undertake here to assess the interrelationship between amyloid load clearance and cerebral blood flow by analysing the MRI arterial spin labelling images and the PET florbetapir images of healthy and AD subjects. From our aforesaid causation analysis approach, we find in this study that (i) increasing serum cholic acid lessens amyloid level in brain (ii) decrease of brain amyloid enhances cerebral perfusion rate in brain. From analysis of animal models and signaling pathway formulation, we found that both the causal process (i) and (ii) have molecular biology-based rationale and framework (Figure 23). We also elucidate the feasible biochemical and biophysical basis of both the causal pathways, based on collateral in vivo investigation.

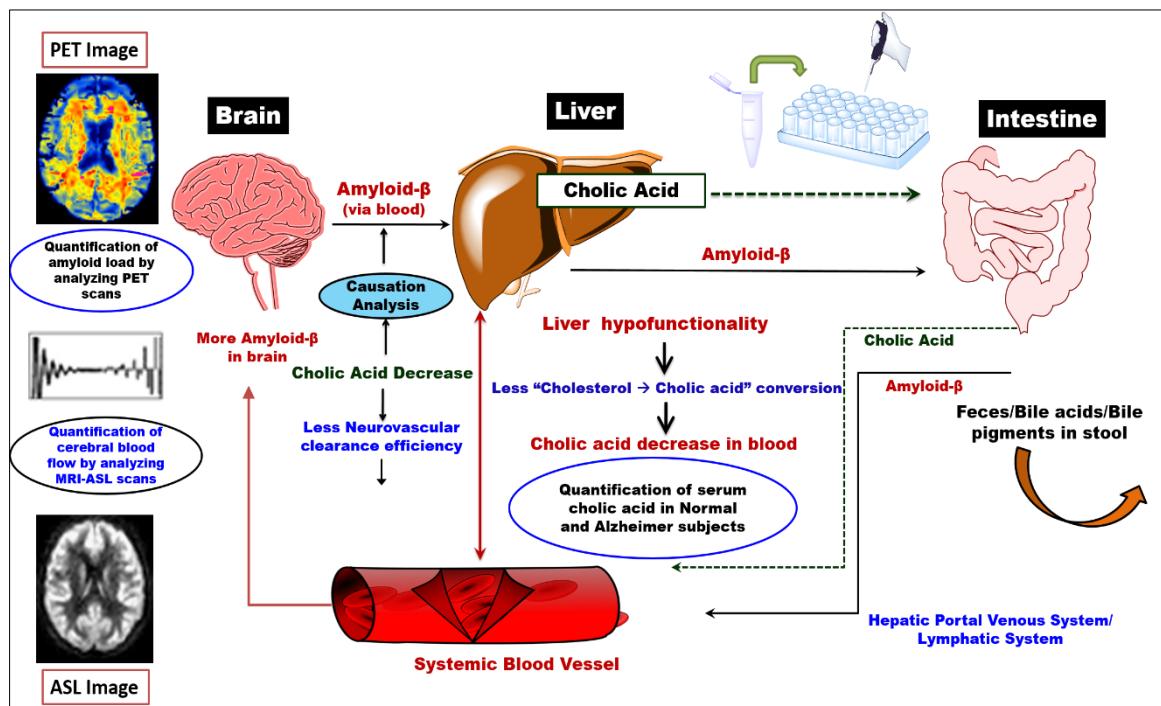


Figure 23: Schematic representation of the outcome of this study, underscoring that AD can be taken to be as orchestration of multi-organ pathophysiology, namely that of the brain, liver, vascular system, and alimentary tract.

