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Peroxisome Proliferator Activated Receptor Alpha (PPARα) Agonists: A Potential Tool for a Healthy Aging Brain

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1. Introduction

1.1 Definitions and considerations

Cognitive decline related to advancing age includes many sub-categories of diseases, some more or less well defined and understood. First, there is "normal" cognitive decline, which is gradual and progressive during aging and seems inevitable. When cognitive decline is large enough to disrupt the activities of daily life, a state of dementia is diagnosed. There are several types of dementia according to the etiology of cognitive decline: vascular dementia, which results from a circulatory disorder causing an obstruction of cerebral blood vessels which leads to the progressive degeneration of brain cells due to a lack of oxygen. Vascular dementia represents 20% of all cases of dementia. Lewis body dementia is an accumulation of α-synuclein protein within the cell and it represents 5 to 15% of neurodegenerative diseases. Frontotemporal dementia as the name suggests, is a degeneration of the region of the frontal and temporal anterior cortex. The reasons for this degeneration are not fully understood. Alzheimer's disease (AD) represents the majority of cases of dementia (65%) although its etiology is not known exactly, or rather multi-factorial.

The most accepted theory in the medical community to explain the origin of AD is currently the accumulation of β-amyloid protein in the form of plaques accompanied by neurofibrillary tangles of tau protein that cause neuronal death and loss of brain matter. However, this theory is challenged for many reasons. The high profile failures of anti-amyloid interventions and lack of agreement on which form the β-amyloid is toxic and the mechanism by which this occurs force the scientific community to consider amyloid only as one part of a multi-factorial disease process including a variety of aggravating factors. A recent paper entitled "Changing perspectives on Alzheimer's Disease: Thinking outside the amyloid Box" resume this thinking (D'Alton & George, 2011).

1.2 Alzheimer's disease diagnosis

The clinical diagnosis of AD is based on clinical examination and confirmed by neuropsychological tests and is diagnosed through exclusion. That means if the person

presents a certain profile of cognitive decline and does not match certain criteria (Table 1) the patient is put into the broad category of "probable" AD (Whitehouse, 2008). Within this category there are "typical" Alzheimer and those who are called "atypical" which means that their profile may include some features of vascular dementia or components of Lewis Body dementia. In 2011, the use of brain imaging (Positrons Emission Tomography (PET) and Magnetic Resonance Imaging (MRI)) can optimize the basic clinical diagnosis (clinical and neuropsychological data) of atypical profile, if this kind of technological platform is available. However, it is only at death that the diagnosis can be confirmed by neuropathological brain examination of the abundance of β-amyloid plaques and neurofibrillary tangle, even if the amyloid theory is increasingly questioned. Not surprisingly, neuropathological diagnosis of post-mortem brain does not always correlate with the clinical diagnosis. One classic example is the "Nun Study" from Chicago (Snowdon et al., 1997), in this study, several participants showed abundant neurofibrillary tangles and β-amyloid plaques at the post-mortem analysis, but had not received a clinical diagnosis of AD and were mentally intact during their life. The opposite was also seen i.e. that a person with a clinical AD diagnostic presented an intact brain (no neuropathology) at death.

Diagnosis of probable AD will be posed only :
IF THE PATIENT DOES NOT PRESENT:
Hypothyroidism; other metabolic problem
Vascular problem
Vitamine deficit (Vitamin B12)
Hypercalcemia
Hydrocephalus
Head injury
Psychiatric disorders (depression, schizophrenia)
Structural brain lesion (tumor, injury, blood clot)
Other degenerative disease (Parkinson disease)
Simulation or factitious disorder
Dehydration or other sources of confusion / delirium
Brain infection (HIV, encephalitis, meningitis, syphilis)
Chronic effects of various substances (alchool, drugs)

Table 1. Alzheimer's Disease: diagnosis of exclusion (Adapted from Whitehouse, 2008)

The mismatch between clinical diagnosis and aβ and tau neuropathology at death shakes the causation link and suggests the importance of other aspects in the etiology of the cognitive decline associated with aging.

1.3 Physiopathology: Focus on brain metabolism

In addition to the abnormal protein (aβ, tau, α-synuclein) present in the demented brains, there is also a decrease in brain glucose metabolism in the majority of dementia. The brain is one of the most metabolically active organs. Despite representing about 2% of adult body weight, the brain uses about 23 % of the body's total energy needs. The brain gets its energy from glucose to 97% making it the main energy substrate. Every day, an average human brain consumes approximately 16% of the total oxygen consumption and metabolizes approximately 110 to 145 g of glucose. Over 90% of used glucose is oxidized to ensure the supply of ATP which is vital for the cells and maintenance of synaptic transmission (Henderson, 2008). The determination of the brain glucose metabolism pattern is used in the differential diagnosis of dementia using Position Emission Tomography (PET) imaging with an analog of glucose; ^{18}fluorodeoxyglucose (^{18}FDG). The cerebral glucose hypometabolism in cases of AD has been known since the 1980s with the beginning of PET imaging and represents about 20% reduction but varies between 8 and 49% (reviewed in Cunnane et al., 2011).

In the case of AD, several evidences shows that brain glucose hypometabolism is present in certain regions well before the first clinical signs of cognitive decline, so it is not simply the result of neuronal loss but rather would be responsible for this loss. For example, in a clinical study containing 20 AD patients and 20 young adults (20-39 years old) at risk of developing AD (carrier of the Apolipoprotein E4 allele; ApoE4), small areas of cortical glucose hypometabolism were present in the young participants, especially in the posterior cingulate, parietal, temporal and prefrontonal cortex. These hypometabolic regions were the same in the AD patients but in a more extensive way. This reduction in brain glucose metabolism may be the earliest brain abnormalities yet found in living persons at risk for AD (Reiman et al., 2004).

It is still unclear as to whether or not healthy aging (no cognitive impairment) is associated with reduction in brain glucose metabolism. Cunnane and collegues reviewed the literature on this specific question and they found out that eight studies showed that cerebral glucose metabolism does not decline with healthy aging and nine studies have demonstrated that it does in a proportion of about 18% (Cunnane et al., 2011.)

The reason for this alteration in brain glucose metabolism is not clearly elucidated. It could be a problem in the glucose transport, glucose availability, or a dysfunction in the production of energy derived from glucose. Mitochondria play a central role in producing ATP as the central source of cellular energy, so a dysfunction at the mitochondria level is conceivable.

The brain uses glucose as main energy source but can also use ketones as an alternative energy source in situations of glucose deprivation (fasting, intense physical activity). Ketones refer to 3 molecules: acetoacetate, β-hydroxybutyrate (β-OHB) and acetone. In starvation conditions, up to 60% of the human brain energy requirements can be met by ketones (Owen, 1967). Whether ketone brain metabolism is also decreasing in healthy aging or in AD is not yet known, but Cunnane's team developed a ketone radiotracer (^{11}C-acetoacetate) especially to be able to study brain ketone metabolism in the elderly; studies are ongoing. Based on the fact that ketones are energetic molecules and used by the brain as an alternative to glucose, some studies have demonstrated the ability of ketones to improve some cognitive dysfunction in diabetic hypoglycemia (Page et al., 2009) and even in case

AD (Henderson et al., 2009). Although brain ketone metabolism is less known in the elderly population, fundamental and clinical studies suggests that they could represents an interesting therapeutic potential for cognitive decline (reviewed in Veech et al., 2001)

1.4 Risk factors: Importance of the metabolic condition

In addition to understanding the physiopathology underlying the cognitive decline it is important to know the factors that increase the risk of being affected by a decline in cognitive function to help prevent them. Aging is the main factor and it often say that it is inevitable. It is true that the passage of time cannot be slowing down, but individuals can play a role in modifying their "biological" age or their metabolic condition. Effectively, aging naturally tends to reduce the cognitive functioning but also worsen the metabolic condition. At advanced age, the prevalence of hypertension, dyslipidemia, inflammation, atherosclerosis and diabetes increase. To prevent these metabolic problems, it is highly documented that the adoption of a healthy lifestyle (physical activities and equilibrate diet) through the lifespan is an efficient way (Colcombe et al., 2003, Peters, 2009.) It turns out that having a bad metabolic condition raises up the risk to develop a cognitive disorder (Frisardi et al., 2010) Peripheral problems and brain disorders are often dissociated but a close relationship exist between these two entities.

Having type II diabetes is associated with the increased risk of developing a cognitive disorder. More than 80% of AD patients have type II diabetes or present an abnormal glucose level. Insulin resistance and hyperinsulinemia, two characteristics of type II diabetes, have been shown to have a high correlation with memory impairment and risk for AD. The rising insulin level that occurs with aging is also a strong predicator of cognitive impairments, in non-diabetics. (Landreth et al., 2008). The Italian Longitudinal study on aging shows that patients with mild cognitive impairment who were also afflict by metabolic syndrome had a higher risk of progression to dementia compared with those without metabolic syndrome. Hypertriglyceridemia was the major component of metabolic syndrome related to dementia (Solfrizzi et al., 2009). Genetic studies and epidemiological observations strongly suggest a relationship between dyslipidemia and AD. Elevated serum cholesterol levels have been reported to correlate with an increased incidence of AD (Landreth et al., 2008). Longitudinal studies have reported that obesity and chronic hypertension are also associated with higher risk of cognitive decline (reviewed in Frisardi et al., 2010).

Then, improvement in those metabolic parameters could modify the individual risk for dementia. Preventive activities during the lifespan are primordial but changing individual behaviour is a long term challenge for the public health. The use of metabolic regulator as a secondary prevention may become essential in individuals at middle age who presents a poor metabolic condition (high blood glucose, deteriorated lipids profile, hypertension, etc.) not only to prevent heart diseases but precisely to delay the first signs of cognitive decline. Given that tertiary prevention of AD dementia which refers to anticholinesterase drugs is known to modestly delay progression of dementia because its probaby too late to correct the existing damage, primary and secondary prevention are essentials (Haan & Wallace 2004) (figure 1).

It is well known that if you want to avoid a pulmonary cancer you should not smoke cigarettes, but the population feels armed less in front of neurodegenerative disorders and should not: progression to dementia can be prevented or modified (Haan et Wallace 2004).

2. PPARα

2.1 Mecanisms, pathways, activators

Peroxisome Proliferator Activated Receptor alpha (PPARα) is a nuclear receptor present in tissues where fatty acids catabolism is at elevated rate, especially in liver but also in heart, kidney, skeletal muscles, enterocytes and astrocytes. This receptor is activated by fatty acids and their derivates and among the synthetic ligands; by compounds of the fibrate family. PPARα regulates gene expression by associating with his ligand in the cytoplasm of cells; the complex then migrates into the nucleus and binds with the 9-cis retinoic acid receptor (RXR). The heterodimer (PPARα/RXR) recognizes specific response elements (peroxisome proliferator response element; PPRE) presents in the promoter regions of genes and binds to activate or repress (figure 2).

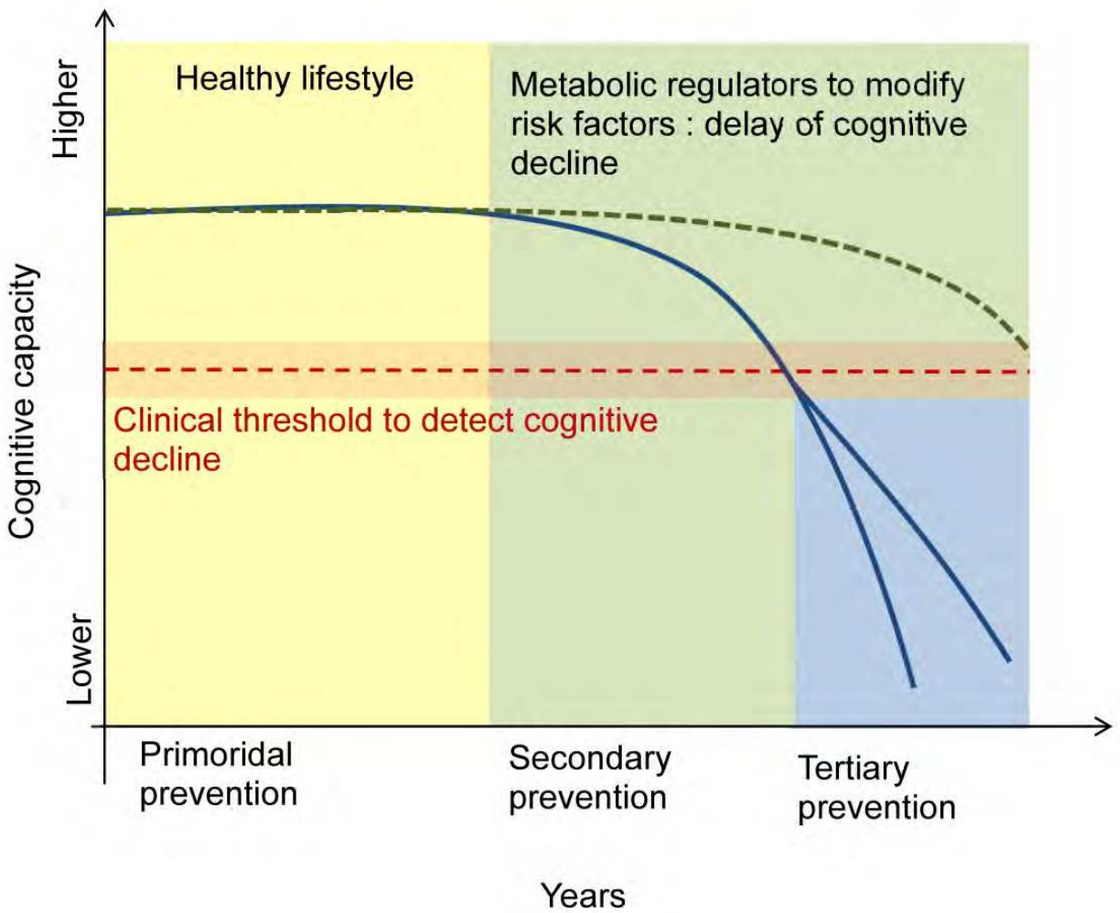


Fig. 1. Schematic cognitive capacity during life. Primordial and secondary preventions, by regulating metabolic condition, may maintain cognitive capacity above the clinical threshold of cognitive decline. Tertiary prevention can modestly help to delays progression of dementia once it is installed. Progression of cognitive capacity in Alzheimer's disease (___) and in cognitively healthy elderly (_ _).

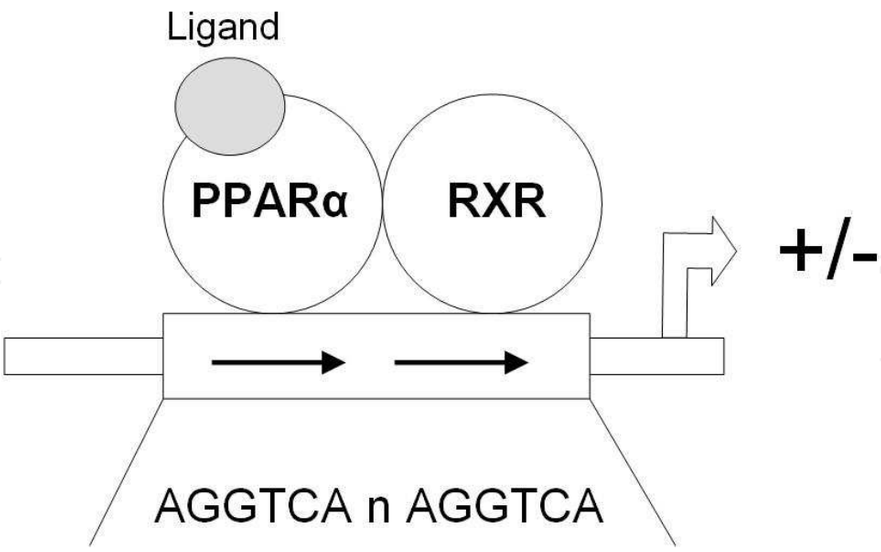


Fig. 2. Following activation with the ligand, PPARα binds a specific DNA sequence (PPRE) in the promoter region of target genes.

PPARα regulates gene associated with lipids, glucose and energy metabolism and exert an anti-inflammatory activity (table 2). Fibrates are first-line drugs used for over 40 years to treat hypertriglyceridemia and their mode of action is entirely via the activation of PPARα. Effectively, fibrates reduces plasma level of triglycerides by 30-50%, slightly increase HDL-cholesterol by up to 5-15 % and usually reduces LDL-cholesterol by 15 to 20% (Chapman et al., 2006). By the activation of PPARα, fibrates are effective to stimulate lipolysis, to increase cellular and mitochondrial fatty acid uptake, to promote fatty acid oxidation, to reduce TG production by the liver, to increase the VLDL clearance and to increase the HDL-cholesterol synthesis.

Genes	Expression	Functions
Apolipoprotein CIII	↓	VLDL clearance inhibition
Lipoprotein Lipase	↑	Lipolysis
Apolipoprotein AI AII	↑	HDL cholesterol synthesis
SR-BI/CLA-1 receptor	↑	Cholesterol efflux
Fatty Acid Binding Protein	↑	Fatty acids entry into the cell
AcylCoA Synthase	↑	Fatty acids entry into the mitochondria
AcetylCoA carboxylase	↓	Fatty acids synthesis
Fibrinogen	↓	Blood clotting
C reactive protein	↓	Inflammation
Interleukin 6	↓	Inflammation
Cyclooxygenase-2	↓	Arachidonic acid metabolism
VCAM-1	↓	Adhesion molecules

Table 2. Target genes regulated by PPARα (Goldenberg et al., 2008). Abbreviations: VLDL: very low density lipoprotein. SR-BI/CLA1: class B scavenger receptor. VCAM-1: vascular cell adhesion molecule 1.

Clofibrate is a first generation fibrate and was used for numerous years before the arrival of the second generation comprising bezafibrate and fenofibrate which are more selective and causes fewer side effects (figure 3). Clofibric acid and fenobibric acid (active metabolites of clofibrate and fenofibrate) activate PPARα and PPARγ but they are 10 times more selective to PPARα. Bezafibrate activates PPARα but can also be linked to PPARγ and PPARδ.

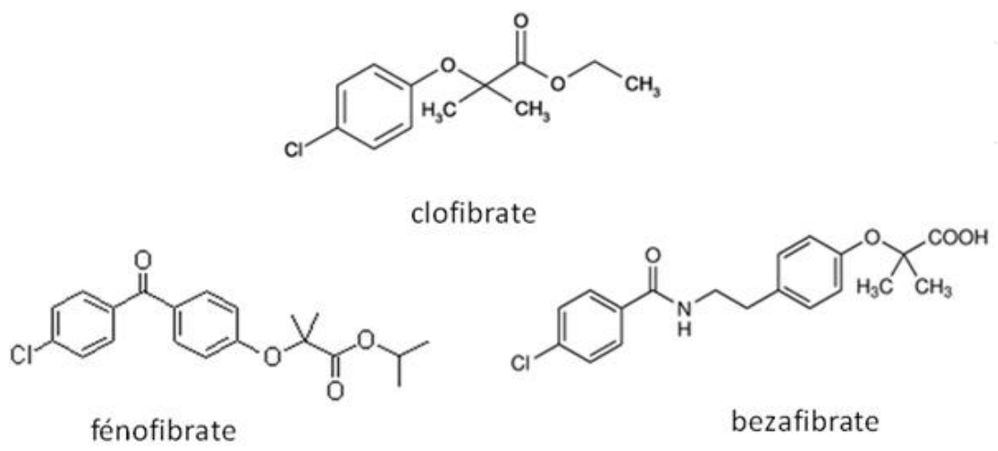


Fig. 3. Structures of clofibrate, fenofibrate and bezafibrate.

2.2 How can PPARα stimulation help cognitive functioning?

The impact of PPARα agonists on cognition was not deeply investigated at a large scale level but some observational studies are interesting. In a large Europeean study (8582 subjects) fibrate use tended ($p=0.07$) to be associated with a reduction in the prevalence of dementia. Dementia included AD (65%), vascular dementia (12%), mixed dementia (11%) and other form of dementia (11.7%). Prevalence of dementia was 1.5% among fibrates user and 2.3% among non-user (Dufouil et al., 2005). In another observational study Rodriguez et al, showed that in a population of 845 individuals, 20.1% of the cohort were demented (based on Clinical dementia Rating) and the proportion of lipid lowering drugs user within the demented population was lower compared to the non-demented (3.5% versus 10.8%) which suggest that lipid lowering drugs may be protective (Rodriguez et al., 2002). In an older study, reducing triglycerides with gemfibrozil (a fibrate) appeared to improve cerebral perfusion and cognitive performance compared to untreated group (Rogers RL et al., 1989). Next sections will focused on how fibrates intake can be protective for the aging brain.

2.3 Insulin resistance

Insulin is produce by the pancreas and control blood glucose level by allowing the transport of glucose molecules from the circulation into cells. Insulin resistance occur when the cells (insulin receptors) are progressively unable to have a proper insulin response resulting in an inadequate entry of glucose in the cells. By a compensatory mechanism, pancreas will secretes more insulin. If the higher amount of insulin is still inefficient to control blood glucose, the person with high insulin and high glucose level will present a situation of pre-diabetes and insulin resistance. Eventually, pancreas will decrease the insulin secretion,

consequence of a pancreatic cell stress and damage, and insulin level will gradually drop and glucose will stay high: type II diabetes is then diagnose. If not treated well, diabetic patient will present high circulating glucose level that can causes deleterious effects including cardiovascular disease, kidney disease, nerve damage, retinopathy, etc. This condition will also lead to deficits in cellular energy production, increased oxidative stress and reduced neuronal survival.

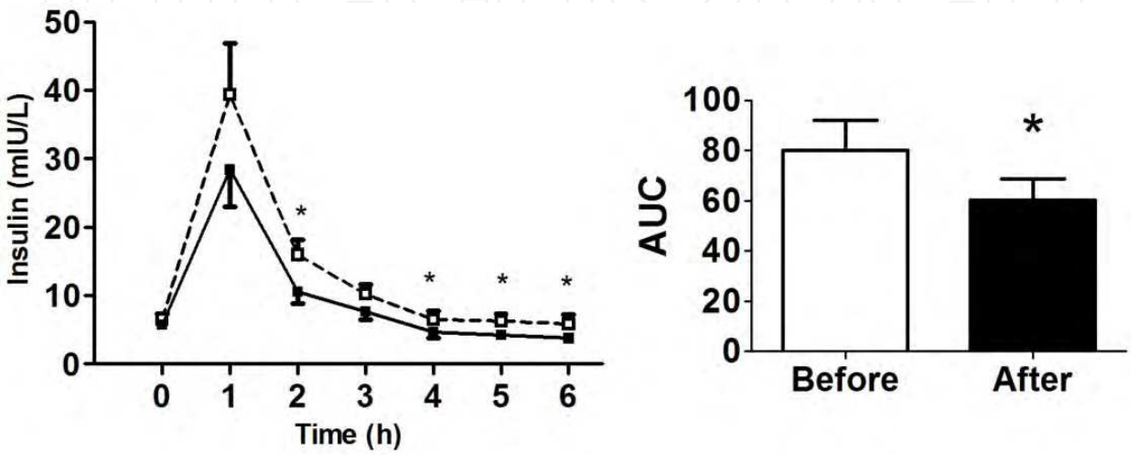
For a long period of time, brain glucose metabolism was known to be independent of insulin action since brain glucose transporters (GLUT-1 and GLUT-3) are insensitive to insulin. Recent literature shows that GLUT-4 responds to insulin and that insulin is produce within the brain in various regions especially in the hippocampus which is associated with learning and memory. Insulin receptors are also presents in the brain (de la Monte et al., 2006). Given that brain cells are dependent on a high glucose supply, brain and peripheral insulin may then play an essential role in brain glucose homeostasis.

Evidences showed a physiological link between insulin and cognition. Reports have documented that brain insulin receptor signaling is reduced in AD brain (reviewed in Rupinder K et al., 2011). Production as well as neuronal insulin receptors was also greatly lower in AD brain compared to age-matched controls (Zhu et al., 2005). Interestingly, in AD patients, peripheral administration of insulin improved memory and cognition, reduced brain atrophy and dementia severity (Burns et al., 2007). In an experimental animal model, intracerebral streptozotocine injection was used to deplete brain insulin, but not pancreatic insulin. This brain specific depletion was associated with progressive neurodegeneration with similar features of AD. This same experiment demonstrates that early treatment with PPARα agonist can effectively prevent this experimentally induced neurodegeneration and the related deficits in learning and memory. This same research team also showed that AD is associated with major impairements in insulin gene expression and that abnormality increase with the severity of dementia. They suggest that AD brain may represent a brain specific form of diabetes; type 3 diabetes (de la Monte et al, 2006).

Hyperlipidemia and fatty acids overload (lipotoxicity) contribute to insulin resistance phenomenon (Reviewed in Carpentier, 2008). By their reducing action on triglycerides and their role in enhancement of fatty acids β-oxidation, PPARα activators should improve insulin sensibility. At human level, findings from a study deriving from Bezafibrate Infarction Prevention trial (BIP) suggest that treatment with fibrate reduce the incidence by 30% and delay the onset of type II diabetes. However, there is not a clear consensus regarding the direct impact of fibrate on insulin sensibility, but from studies reviewed, 10 showed an improvement (Tenenbaum et al., 2007, Cree et al., 2007, Kim et al., 2003, Damci et al., 2003, Jonkers et al., 2001, Idzio-Wallus, 2001, Yong et al., 1999, Kobayashi et al., 1988, Murakami et al. 1984, Ferrari et al., 1977) and 6 a reduction in sensibility or no change (Anderlova et al., 2007, Rizos et al., 2002, Whitelaw et al., 2002, Asplund-Carlson, 1996, Sane et al., 1995, Skrha et al., 1994) . In a recent study (2010) bezafibrate treatment for 12 weeks in a mild hypertriglyceridemic population showed a postprandial insulin response 26% lower after bezafibrate, suggesting the beneficial impact of fibrate on insulin sensitivity (figure 4; Tremblay-Mercier et al., 2010). Further clinical studies measuring insulin sensibility are warranted to confirm the real insulin-sensitizing potential of fibrates and the subsequent impact on brain glucose metabolism and further impact on cognition.

2.4 Ketone production

Ketones are the alternative fuel for the brain when glucose availability is low to insure an optimal brain functioning. They are the product of triglycerides lipolysis, β-oxidation of fatty acids and ketogenesis (figure 5). The majoritary of ketones are synthesised in the liver. Studies have shown that astocytes have the capacity to produce ketones from fatty acids and the ketogenic system (Auestad et al. 1991; Guzman & Blazquez, 2001). Acetyl CoA resulting from the β-oxidation of fatty acids, undergo the Krebs cycle but if the metabolic context is favorable for the ketone body formation, acetyl CoA will be redirected in the ketogenesis pathway.



A B

Fig. 4. A) Insulin concentration (mIU/L) during 6 hours. Breakfast was taken between time 0 and time 1 with no further meal. Before (-□-) and after (-■-), 12 weeks on bezafibrate. B) Area under the curve of the insulin curves were lower after bezafibrate treatment. Data are expressed by mean ± SEM. n=12, * p≤0.05. (Adapted from Tremblay-Mercier, 2010)

Under normal conditions (regular meals) ketogenesis is at a low rate (ketone bodies concentration <0.1 mmol/L), because a slight rise in blood glucose and the following increase in insulin concentration inhibits lipolysis and ketogenesis. After their production, β-OHB and acetoacetate will reach skeletal muscles, brain and heart by the systemic circulation to provide energy. Ketones will then be retransformed into acetyl CoA by the reaction called ketolysis (figure 6). Liver cannot use ketones as energetic molecules because the enzyme β-ketoacyl-CoA transferase is not present in the liver, so ketolysis can not occur (figure 6). Ketones pass through the blood brain barrier (BBB) by facilitated transport following the concentration gradient by the monocarboxylate transporter 1 (MCT-1), as well as pyruvate and lactate. The rate of cerebral ketone metabolism depends primarily on the concentration in blood. Cerebral ketone metabolism is also regulated by the permeability of the BBB, which depends on the abundance of MCT-1. An increase in ketone body concentration up regulates the expression of MCT-1 transporter (Leino et al. 2001; Pifferi et al., 2011).

In vitro experiments show that β-OHB protects hippocampal neurons in culture against the toxicity of the protein β-amyloid 1-42, found in the senile plaques in AD patients. This protective effect may be partly due to the fact that the ketone metabolism does not require the action of the enzyme pyruvate dehydrogenase (PDH) which is affected by the toxic

effect of β-amyloid protein and essential for the conversion of glucose into energy (Kashiwaya et al., 2000). Rats and human studies also showed that ketones decreased damages associated with free radical (Sullivan et al., 2004)

Ketone production can be stimulated by fasting but also by the administration of a ketogenic diet. This classic ketogenic diet contains a 4:1 ratio by weight of lipids to combined glucose and protein; this high fat intake forces the body to burn fatty acids rather than glucose. The therapeutic ketogenic diet was developed for treatment of pediatric epilepsy refractory to anticonvulsant in the 1920s. This diet is very effective to treat epilepsy in 30-50% of cases but is very hard to apply in a daily basis and causes significant side effects (Cross et al., 2007). Another dietary way to stimulate ketogenesis is by the ingestion of medium chain triglycerides (MCTs), which provokes an acute elevation in ketone body concentration. Those triglycerides are composed of saturated fatty acids from 6 to 12 carbons and are absorbed across the intestinal barrier and directly enter the portal vein. This allows for much quicker absorption and utilization of MCTs compared to long chain triglycerides. MCTs are transported into the mitochondria independent of the carnitine palmitoyltransferase (CPT), which is necessary for the mitochondrial absorption of long chain fatty acids. After a single dose of MCTs, a significant raise (176%) in ketone bodies concentration occur within one hour but rapidly drops to baseline values (within 2 hours) so the effect is transient (Courchesne-Loyer et al., in preparation).

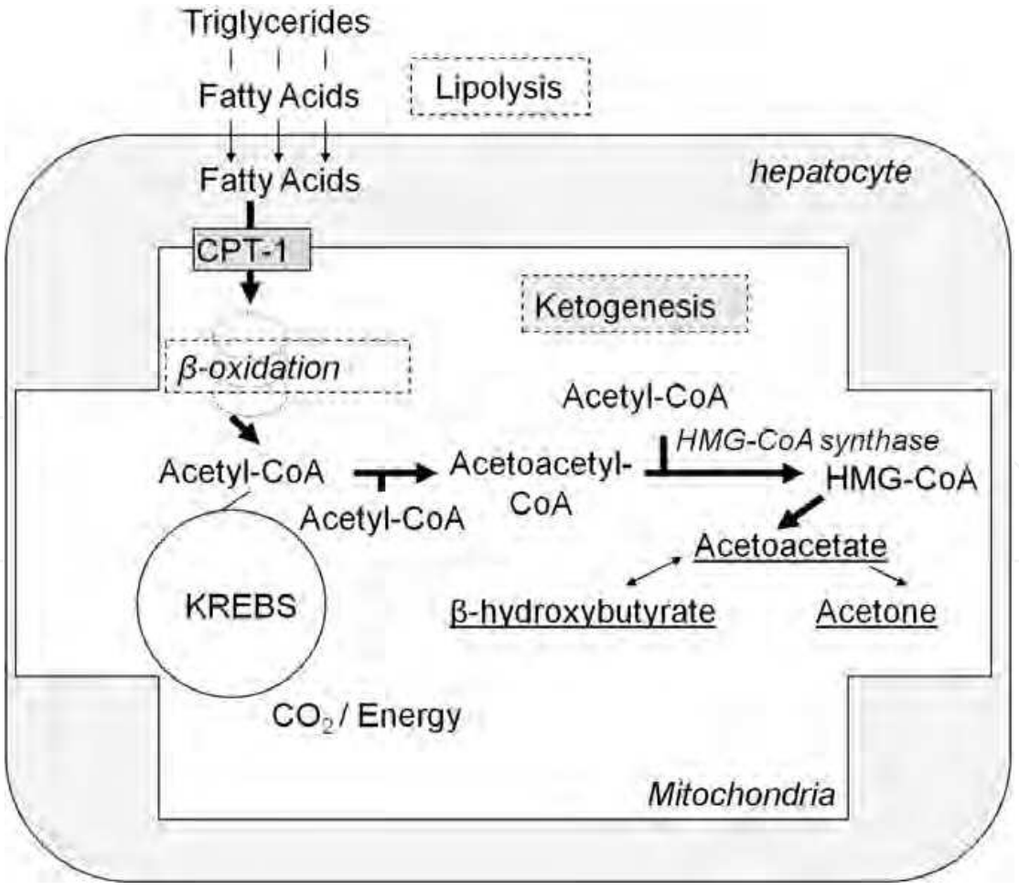


Fig. 5. Ketogenesis pathway. CPT-1: Carnitine palmitoyltransferase 1.

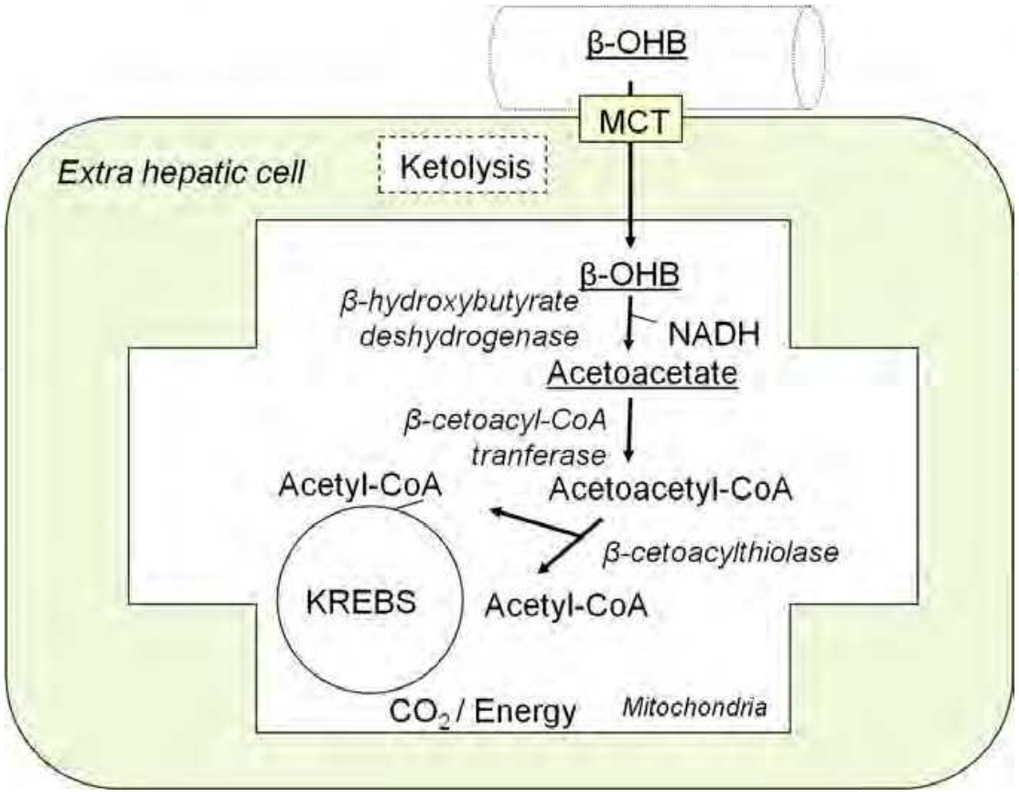


Fig. 6. Ketolysis pathway. β-OHB: β-hydroxybutyrate

Several human studies show that a slight raise in ketones concentration can maintain normal brain function even when plasma glucose would normally be low enough to result in acute cognitive and functional deficits. For example, Page and colleagues in 2009, administered MCTs to type 1 diabetics patient in hypoglycemic crisis and they observed an acute improvement in cognitive functions. Levels of ketones after the ingestion of MCTs were about 0.3-0.4 mM and were sufficient to have an impact on cognitive functioning (Page et al. 2009). Another team showed that a daily supplementation with MCTs for 90 days increased the ketogenic response to 400% and showed a score improvement at different cognitive tests in AD patients (Henderson et al, 2009). In 2004, Reger and colleagues conducted a study with 20 AD patients and showed that high β-OHB concentrations obtained after MCTs administration are positively correlated with ameliorations in the paragraph recall test which is involving memory cognitive function (figure 7).

Ketogenic diet and MCT ingestion, provides low glucose, low insulin environment and/or susbtrates for ketogenesis and are effective in raising ketones concentrations but need a change in eating habits. Another way to increase ketone bodies production without modifying eating habits is to up regulate the enzymes implicated in the pathway. As mentioned earlier fibrate drugs, via PPARα, stimulates the transcription of genes encoding for triglyceride lipolysis and fatty acid β-oxidation. As well, fibrate increase the transcription for the key enzyme in the ketogenesis which is the HMG CoA synthase. This enzyme catalyses the reaction between acetoacetyl CoA and acetyl CoA to form HMG-CoA (figure 4). Few studies on rats have demonstrated an increase in the production of ketone

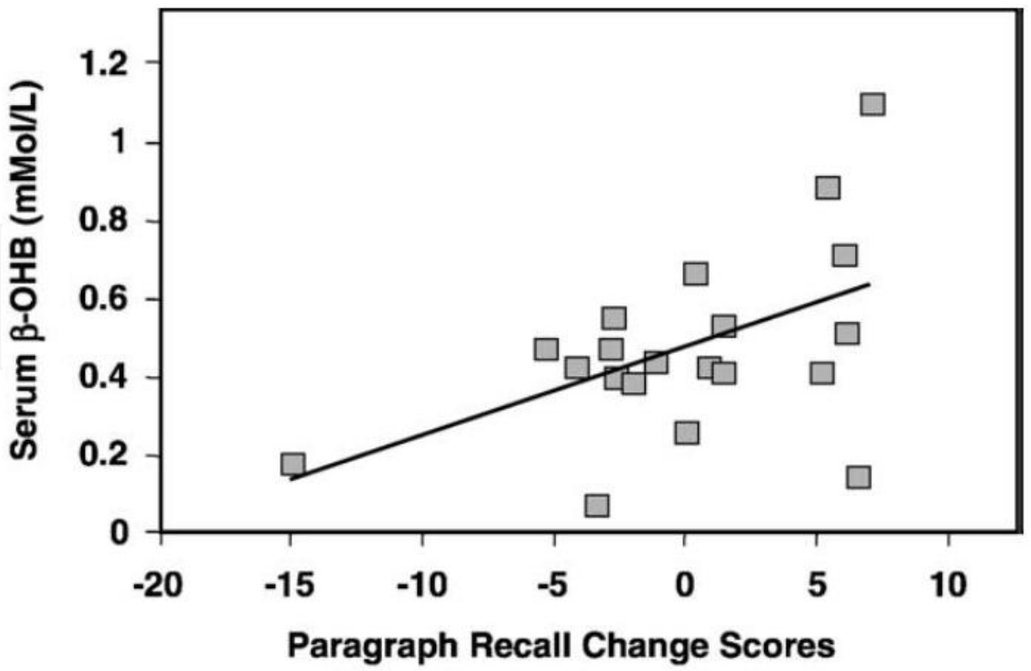


Fig. 7. Relationship between β-hydroxybutyrate (β-OHB) levels at the time of cognitive testing and the change in paragraph recall; $r = 0.50$, $P = 0.02$ (Reger et al., 2004).

bodies by the liver following a fibrate treatment which concord with studies on hepatocytes. In rats treated with clofibrate, PPARα stimulation leads to an upregulation of MCT-1 (König et al., 2008). At the human level the first study to investigate ketone metabolism following a fibrate therapy was done at the Research Center on Aging in Sherbrooke, Quebec, Canada. This study suggests that treatment with bezafibrate has a mild ketogenic potential; postprandial β-OHB response was 58% higher after bezafibrate treatment for 12 weeks. With bezafibrate treatment, the level of ketones (β-OHB) was low during fasting (early in the morning) but was rising during the experimental day to reach 0.3-0.4 mM β-OHB at the end of the day (Tremblay-Mercier et al., 2010). Perhaps in conjunction with a fibrate, joint administration of a dose of MCT, would maintain a moderate level of circulating ketones to insure the delivery to the brain to maintain the energetic homeostasis (Tremblay-Mercier et al., 2010). Preliminary results concerning cerebral ketone metabolism with the tracer ^{11}C-acetoacetate shows that brain ketones uptake is proportional to physiologic plasma ketones concentration as expected by anterior studies (Cunnane et al,. 2011). Further studies with this tracer will help to better understand the impact of fibrate on ketogenesis and the repercussion on brain metabolism in elderly and in cognitively impaired patients.

2.5 Mitochondrial function

Mitochondria are the central organelle in the generation of cellular energy via the Krebs cycle and the electron transport chain. They may be a key players in the cerebral low glucose metabolism observed in AD. Effectively, in the diseased brain, the numbers of neuronal mitochondria are greatly reduced. Several studies have demonstrated aberrations in the electron transport complexes and Krebs cycle in AD (Atamna & Frey, 2007). Mitochondrial

perturbations are also seen in normal aging. Those perturbations decrease activities of complex I and IV of the electron transport chain which lead to an elevated reactive oxygen species production. Increased free radicals and peroxidative damage is also seen in AD (Cunnane et al., 2011). Mitchondria dysfunction seems to contribute to the early stage and to the development of various neurodegenerative diseases (Gibson et al., 2010). Numerous studies have suggested that the activation of PPAR may improve mitochondrial functions. PPARγ stimulation is likely to be more effective than PPARα in inducing mitochondrial biogenesis and seems to be effective to potentiate glucose utilization leading to improved cellular and cognitive function (Rupinder et al., 2011). Fibrates are more selective to PPARα but they also have an action on PPARγ. PPARα play a role in the oxidative stress observed in aging. Effectively, level of PPARα correlated negatively with lipid peroxide levels which are actually reduced following a bezafibrate administration (Pineda Torra et al., 1999). Therapeutic strategies targeted at preventing, delaying or treating mitochondrial dysfunction should contribute to the prevention or treatment of age related neurodegeneratives diseases (Atamna & Frey, 2007), and fibrates may be an interesting target to consider.

2.6 Cardiovascular condition /inflammation

There is a close link between cardiovascular condition and cognitive status. High blood pressure, obesity, hyperlipidemia and diabetes are among the principal risk factors for cardiovascular disease. Having those conditions also increase the risk of developing cognitive decline. Vascular risk factors may impair cognitive functions and are related to the occurrence of AD, hypertension and type II diabetes present the strongest association, especially when these factors are assessed in middle age. Atherosclerosis is also believed to be involved in development of dementia, particularly, vascular dementia. Some investigations have shown the importance of inflammation in the pathogenesis of AD, (Akiyama et al., 2000). Hypercholesterolemia, oxidative stress and inflammation have emerged as the dominant mechanism in the development of both atherosclerosis and AD (Steinberg, 2002).Genetic studies and epidemiological observations strongly suggest a relationship between dyslipidemia and AD. Elevated serum cholesterol levels have been reported to correlate with an increased incidence of AD.

Based on its efficiency to reduce plasma triglycerides and to increase HDL cholesterol and it lowering action on LDL-cholesterol, major randomized intervention trials involving fibrate therapy were done to evaluate the drug efficiency to prevent cardiac events. These studies showed that a treatment with a fibrate has beneficial effects by reducing myocardial infarction and coronary event (Goldenberg et al., 2008). The Bezafibrate Infarction Prevention (BIP) trial in 2000 showed that bezafibrate also prevent atherosclerosis and significantly attenuates the risk of long term major cadiovascular events (Tennenbaum et al., 2005). PPARα is also involved in the anti-inflammatory response by his inhibition of NFκB transcription and by decreasing the production of pro-inflammatory IL-6, prostaglandins and C- reactive protein. Fibrates are known to be efficient molecules to prevent cardiovascular disease, knowing that cardiovascular disease and cognitive decline share the same risk factors, preventing cardiovascular disease with fibrate therapy should help preserving cognitive functioning during aging.

3. Conclusions

Fibrates act as synthetic ligands for PPARα and are commonly used to treat hypertriglyceridemia and to prevent coronary heart disease. PPARα is also involved in the anti-inflammatory response and in improvement of mitochondrial function. Fibrate therapy reduces the incidence and delays the onset of type II diabetes and seems to improve insulin sensibility in humans (Goldenberg et al., 2008). A recent clinical study suggests that in hypertriglyceridemic individuals, bezafibrate increase the production of ketone bodies, the alternative energy source for the brain (Tremblay-Mercier et al., 2010). Thus, by reducing triglycerides, enhancing glucose availability, providing alternative brain fuel and improving cardiovascular profile, PPARα agonist could have relevant impact on the maintenance of a good cognitive health later in life (figure 8). Fibrate therapy may have potential as pharmacological agents aiming to reduce the risk of AD and future research are needed to determine if secondary prevention with fibrate therapy is able to delay the apparition of cognitive decline.

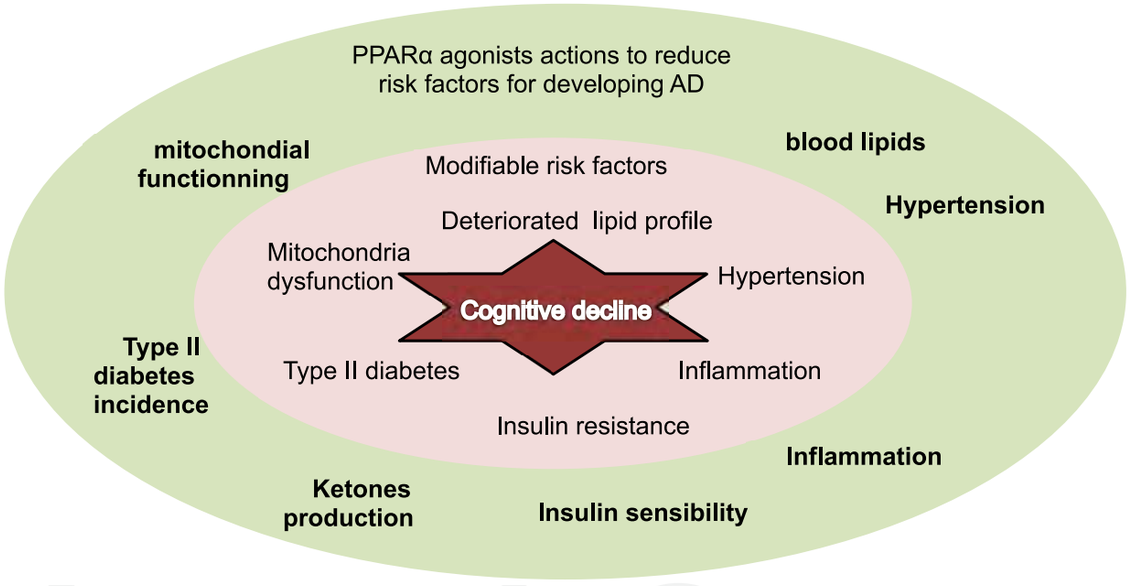


Fig. 8. Summary diagram on the PPARα agonist's action on modifiable risk factors for cognitive decline.

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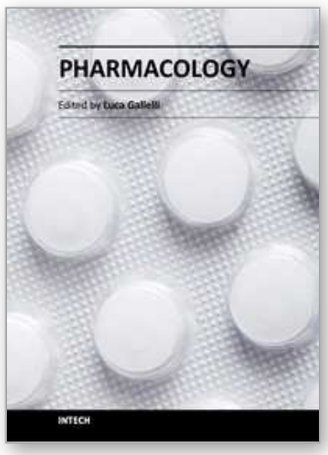

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