Altered d-glucose in brain parenchyma and cerebrospinal fluid of early Alzheimer's disease detected by dynamic glucose-enhanced MRI

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1. 簡訴論文概要及重大發現

阿爾茨海默症(Alzheimer disease, AD) 是一種神經退化性疾病，為老年性癡呆的一種類型，它以多種方式影響患者的日常生活，包括記憶力、說話、解決問題的能力和其他生活技能的障礙。就現階段而言，尚未有特效藥物可以治療，只能延緩病情的惡化。如果能提早發現並採取預防性的治療方法，可以延緩 AD 的發生。目前對於 AD 的診斷方法有三種，分別是電腦斷層攝影(Computed Tomography, CT)、核磁共振成像(Magnetic resonance imaging, MRI)、正電子發射斷層掃描(Positron emission tomography, PET)，其中核磁共振成像是對人體較為無害的檢測方法，所以作者選擇核磁共振成像來開發新型的檢測方式。在舊有的文獻指出，AD 病患大腦 glucose 的代謝方式有別於正常大腦，因此作者想利用這點，特別針對 D-glucose 進行觀察。作者利用 Dynamic Glucose Enhanced (DGE) Imaging 的 檢測方式，發現 AD 小鼠組別中，年輕小鼠的 D-glucose 攝取量大於年老的小鼠，而在同為年輕小鼠的情況下，AD 小鼠的 D-glucose 攝取量也大於 WT 小鼠。作者最後證明了 DGE 是可以觀察不同腦區的代謝狀態，且可以同時收取腦組織及腦脊髓液的 D-glucose 訊號，並且有助於預判 AD 的生成。

2. 對論文內容的提問

AD 小鼠年齡與 D-glucose 有依賴性，且年齡與吸收率成正比；與信號強度成反比；但與清除率沒有年齡的依賴性。所以這是否暗示著，年輕 AD 小鼠的 SMAX 高是因為，AD 的過表達還沒有開始所以腦部結構還沒有病變，可以接收到 D-glucose 量就比較多，但實際能吸收的量是有限的，因此造成吸收率比較低的現象；反之老年的 AD 小鼠，因為 AD 的過表達造成腦部結構發生病變，能接收到的 D-glucose 量變少，但少量的 D-glucose 剛好與實際能吸收的量差不多，所以造成吸收率較高的現象。

3. 論文的缺點與評論

本篇作者證明了 Dynamic Glucose Enhanced (DGE) Imaging 可以判斷 AD 小鼠的發病前後代謝的差異。近年來，也發現不同腫瘤的代謝途徑不竟相同，希望可以用 Dynamic Glucose Enhanced (DGE) Imaging 來觀察不同腫瘤中的代謝，藉此幫助醫師在臨床上更加準確的判斷。

NEUROSCIENCE

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Altered cerebral glucose uptake is one of the hallmarks of Alzheimer's disease (AD). A dynamic glucose-enhanced (DGE) magnetic resonance imaging (MRI) approach was developed to simultaneously monitor D-glucose uptake and clearance in both brain parenchyma and cerebrospinal fluid (CSF). We observed substantially higher uptake in parenchyma of young (6 months) transgenic AD mice compared to age-matched wild-type (WT) mice. Notably lower uptakes were observed in parenchyma and CSF of old (16 months) AD mice. Both young and old AD mice had an obviously slower CSF clearance than age-matched WT mice. This resembles recent reports of the hampered CSF clearance that leads to protein accumulation in the brain. These findings suggest that DGE MRI can identify altered glucose uptake and clearance in young AD mice upon the emergence of amyloid plaques. DGE MRI of brain parenchyma and CSF has potential for early AD stratification, especially at 3T clinical field strength MRI.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, accounting for 60 to 70% of this disease. It affects the patients' daily life in many ways, including impairments in memory, speaking, problem solving, and other basic life skills (*1*). Early AD stratification remains challenging because changes in current biomarkers often overlap with normal aging. Neuropathology of AD includes the overexpression of amyloid precursor protein (APP) that results in the deposition of β amyloid (Aβ) plaques and tau neurofibrillary tangles, thus leading to structural and functional brain abnormalities in AD (*1*). Recent findings suggested that a reduction in cerebrospinal fluid (CSF) transport is associated with elevated brain Aβ, especially in young AD mice without visible Aβ plaques (*2*). Moreover, a change in cerebral glucose uptake is one of the hallmarks of AD (*3*). Glucose hypermetabolism or hypometabolism in brain has been found in some AD mouse models in different stages of AD (*4*–*7*). Luo *et al.* and Poisnel *et al.* (*5*, *6*) both observed a higher glucose utilization in brains of young APP mice but a lower glucose utilization in aged APP mice compared to the age-matched wild-type (WT) mice. Many AD drugs are being developed using transgenic mouse models of amyloidosis-expressing mutant forms of human APP and presenilin-1 (PS1) (*8*), which is well known to reproduce some of the neuropathology observed in humans. Thus, glucose utilization and CSF clearance serve as important imaging biomarkers for early AD stratification.

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Currently, glucose uptake and metabolism can be assessed spatially by administering a radioactive glucose analog, 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}FDG), and imaging with positron emission tomography (PET) (*9*). Although ^{18}FDG-PET can detect the altered glucose usage with great sensitivity, the high cost and still limited availability in hospitals of PET-CT (computed tomography) hamper its general clinical application. Moreover, the use of radioactive tracers in combination with the additional ionizing radiation of CT detection is not ideal for repeated measurements. Recently, it has become possible to image sugars with magnetic resonance imaging (MRI), exploiting the interaction between hydroxyl protons and water (*10*, *11*). The dynamic imaging of glucose uptake and utilization, named dynamic glucose-enhanced (DGE) MRI, contains information regarding glucose delivery, tissue transport, and metabolism (*12*–*19*). Tolomeo *et al.* (*7*) used DGE MRI to monitor altered glucose uptake in AD mouse brain with 2-deoxy-D-glucose (2-DG) at 7T. They found a lower 2-DG uptake in one AD mouse model (APP23). To facilitate translation to clinical AD diagnosis, however, it is necessary to implement DGE MRI at a 3T clinical field strength (*20*, *21*) and to use nontoxic sugars. We therefore designed an adjusted on-resonance variable delay multiple pulse (onVDMP) MRI (*22*) approach (see Materials and Methods and fig. S1A) to dynamically detect D-glucose delivery, uptake, and utilization in mouse brain on a 3T MRI animal scanner. By adjusting the length of the saturation module of onVDMP MRI, we were able to simultaneously monitor brain parenchyma and CSF in the APP/PS1 and WT mouse brains for two age groups [6 (6M) and 16 months (16M)]. Studying CSF is of interest because recent findings have shown that abnormality of the glymphatic system, a paravascular route for CSF flow through the brain parenchyma, could be a possible feature of AD (*23*, *24*). A typical glymphatic system, which is shown in Fig. 1, is defined as a brain-wide paravascular pathway for CSF and interstitial fluid (ISF) exchange that facilitates efficient clearance of solutes and waste from the brain. Therefore, in addition to brain parenchyma, we studied the uptake and clearance of D-glucose in