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Changes in regional cerebral blood flow associated with a 45 day course of the ketogenic agent, caprylidene, in patients with mild to moderate Alzheimer's disease: Results of a randomized, double-blinded, pilot study

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ABSTRACT

Background: Caprylidene is a ketogen that, when metabolized, produces the ketones beta-hydroxybutyrate and acetoacetate, which can cross the blood brain barrier. It has been hypothesized that ketone bodies can be used as an alternate energy source by neurons with impaired glucose utilization. Caprylidene has been shown to improve cognition in patients with mild-to-moderate Alzheimer's disease (AD) who lacked an AD-predisposing allele (ε4) of the gene for apolipoprotein E. In this pilot study, we examined the effects of caprylidene on regional cerebral blood flow (rCBF) in patients with mild to moderate AD.

Methods: Sixteen subjects with mild-to-moderate AD, based on NINCDS-ADRDA criteria, were enrolled in a double-blinded, placebo-controlled, randomized clinical trial. Fourteen subjects received treatment with caprylidene, and 2 subjects were given placebo. Subjects received 4 ^{15}O-water PET scans over the course of the study to assess rCBF: once before receiving a standard caprylidene or placebo dose and 90 min after the dose, on the first day and after 45 days of daily caprylidene or placebo consumption. The scans were examined by standardized volumes of interest (sVOI) and voxel-based statistical parametric mapping (spm) methods of analysis.

Results: Subjects lacking an ε4 allele had significantly elevated rCBF in the left superior lateral temporal cortex by sVOI analysis after adopting a caprylidene diet for 45 days ($p = 0.04$), which was further corroborated by spm. The anterior cerebellum, left inferior temporal cortex, and hypothalamus were also found by spm to be regions of long-term increase in rCBF in these subjects. In contrast, patients who possessed the ε4 allele did not display these changes in rCBF.

Conclusion: Daily ingestion of caprylidene over 45 days was associated with increased blood flow in specific brain regions in patients lacking an apolipoprotein ε4 allele.

1. Introduction

Alzheimer's disease (AD) is considered to be the most common cause of neurodegenerative dementia, currently affecting about 5.7 million Americans (Alzheimer's Association 2018). The number of patients with AD is expected to increase dramatically, to approximately 13.8 million by 2050 (Alzheimer's Association 2018). AD is characterized by extracellular neuronal accumulation of beta-amyloid plaques and intracellular neuronal accumulation of tau protein in neurofibrillary tangles (Caselli et al. 2017). These accumulations are associated with diminished synaptic communication and neuronal death, resulting in impairments in memory, thinking, and daily functioning. AD is associated with a progressive course of cognitive and functional decline, ultimately resulting in death, often secondary to pneumonia as the

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presumed cause (Brunnström and Englund 2009). Despite worldwide efforts to find a cure for AD, current pharmacological treatments are limited and can only temporarily improve cognition and function, or delay their decline (Eleti 2016). Though the underlying causes of AD occurring after 65 years old remain to be well-established, the strongest genetic risk factor that has been identified in this age group is carriage of the ε4 allele of the gene for apolipoprotein E (APOE4).

Caprylidene is a medium-chain triglyceride of caprylic acid that results in the production of ketone bodies, including beta-hydroxybutyrate and acetoacetate, after oxidation by the liver (Costantini et al., 2008). These ketone bodies can cross the blood-brain barrier and may be used as an alternate source of energy by neurons that exhibit impaired glucose utilization. In turn, the increased energy may improve neuronal survival and improve cognitive function (Cunnane et al. 2016; Sharma et al. 2014). Clinical trials have demonstrated highly elevated serum beta-hydroxybutyrate levels following caprylidene supplementation (Reger et al. 2004), and have found a significant difference in ADAS-Cog scores between active and placebo groups in caprylidene, previously formulated as Axona® (Accera, Inc., Boulder, CO), with the difference mainly driven by a decline in scores in the placebo group (Henderson et al. 2009). However, the exact neurobiological effects of caprylidene remain to be established.

The primary objective of this study was to evaluate acute and long-term effects of caprylidene on regional cerebral blood flow (rCBF) in mild-to-moderate AD subjects. An additional objective was to examine any differences in effects of caprylidene on rCBF between APOE4-positive and APOE4-negative subjects.

2. Material and methods

2.1. Patients

Sixteen subjects with mild-to-moderate AD were enrolled in a double-blinded, placebo-controlled, randomized, clinical trial to assess neurobiological effects of caprylidene. Eligible subjects were between ages 50–90 who had MMSE scores in the range of 10–28 and a diagnosis of probable AD based on NINCDS-ADRDA criteria (McKhann et al., 1984). The subjects were randomized with 14 subjects receiving treatment with caprylidene, and two subjects receiving placebo, as further detailed below.

Participants underwent four ^{15}O-water PET scans, two scans on the first day (Day 1) and two scans after 45 days of daily caprylidene or placebo consumption (Day 45). On Day 1, each subject was scanned before receiving a 40-gram dose of caprylidene or a matching placebo formulation (Scan 1) and 90 minutes post-dose (Scan 2). On Day 45, subjects were scanned before receiving the last dose of caprylidene or placebo (Scan 3) and 90 min post-dose (Scan 4) (Fig. 1). Acute effects of a single dose of caprylidene on treatment-naïve participants (no prior history of caprylidene use before Day 1) and post-treatment (after 45 days of daily caprylidene supplementation) were tested by comparing Scan 1 versus Scan 2 and Scan 3 versus Scan 4, respectively. Long-term effects of a ketogenic diet were tested after 45 days of daily caprylidene supplementation through comparisons of the pre-dose scans (Scan 1 versus Scan 3) and the post-dose scans (Scan 2 versus Scan 4). Long-term changes in acute responses (Scan 2- Scan 1) versus (Scan 4-Scan 3) were also tested.

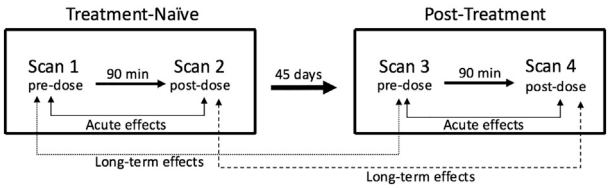

Fig. 1. All subjects underwent 4 PET scans (15O-H2O). Two scans were performed on the first day in treatment-naïve patients (no prior intake of caprylidene), with Scan 2 performed 90 min after a single dose of caprylidene. Two subsequent scans were performed post- treatment (after 45 days of caprylidene supplementation), with Scan 4 performed 90 min after a final dose of caprylidene. Scan 1 versus Scan 2 and Scan 3 versus Scan 4 were used to evaluate for acute changes, while Scan 1 versus Scan 3 and Scan 2 versus Scan 4 were used to evaluate for long-term changes.

Analyses were performed for all participants receiving caprylidene, as well as for subgroups stratified by APOE4 status. For the stratified analysis, subjects who carried at least one copy of APOE4 gene were grouped as APOE4-positive. Data from the placebo arm, comprised of only six scans and two subjects, were not used for any of the analyses reported here; rather, this group played a methodologic role to ensure rigorous double-blinding of participants and investigators, since no subject nor investigator knew before completion of the protocol whether a subject had been randomized by the pharmacy to active or placebo formulation.

2.2. Imaging protocol

PET scans were acquired dynamically, beginning immediately after intravenous administration of 555 MBq [15O] water, using an HR+ Siemens/CTI scanner. The data from the time the tracer bolus reached the brain (approximately 25 s after administration) to 120 s were then summed to derive the images. PET images were reconstructed using filtered back projection and transmission-based attenuation correction obtained with a rotating rod source.

2.3. Data analysis

The images were realigned, normalized and smoothed using the voxel-based statistical parametric mapping program, SPM12. The scans of subjects across all subjects receiving caprylidene were compared using paired *t*-tests voxel by voxel. Five comparisons paired by subject were selected for analysis: Scan 1 vs Scan 2, Scan 3 vs Scan 4, Scan 1 vs Scan 3, Scan 2 vs Scan 4 and (Scan 2 - Scan 1) vs (Scan 4 - Scan 3). These comparisons were also performed for each APOE4-based subgroup. Differences at the cluster level of analysis reaching $p < 0.05$, after statistical correction for multiple comparisons by false discovery rate (FDR) were considered significant. Cluster size was assessed as the number of contiguous voxels with intensity differences having p-value below 0.01 before statistical correction.

The rCBF data were also analyzed by quantifying 47 standardized volumes of interest (sVOI) using the FDA-cleared commercially available brain quantification software package, NeuroQ™ (Syntermed, Inc., Atlanta, GA), as derived by dividing the mean counts per second per pixel in each sVOI by the mean counts per second per pixel across all assessed regions in the brain (n = 240). Mean uptake ratios along with standard deviation of each sVOI in each scan were calculated, and paired *t*-tests were used to evaluate for differences in mean uptake ratios of each sVOI within APOE4-positive and negative subgroups as well as across all subjects undergoing caprylidene therapy. Comparisons identical to those performed by spm (i.e. Scan 1 vs Scan 2, Scan 3 vs Scan 4, Scan 1 vs Scan 3, Scan 2 vs Scan 4 and (Scan 2 - Scan 1) vs (Scan 4 - Scan 3) were performed. Differences with p-value of < 0.001 in each sVOI allowing for statistical correction for multiple comparisons were considered significant.

3. Results

3.1. Subject characteristics

In total, 54 PET scans were acquired from 16 subjects. Among the fourteen subjects receiving active caprylidene treatment, five of eight who were APOE4-positive and five of six who were APOE4-negative completed all four PET scans. The remaining four subjects completed two of the four planned PET scans. All available scans were analyzed in

each comparison described. Among those receiving active caprylidene treatment, average age was 79.9 ± 9.2 (mean ± SD), average education was 14.8 ± 3.1 (mean ± SD), and 70% were females. Baseline MMSE and ADAS-Cog scores were 21.1 ± 7.0 (mean ± SD) and 23.4 ± 10.1 (mean ± SD), respectively.

3.2. Imaging analysis

After correction for multiple comparisons, sVOI analyses demonstrated no significant acute or long-term changes in rCBF, assessed across all subjects. When stratifying the data by subjects' genotype, the APOE4-negative subgroup (age 79.4 ± 5.3 yrs., mean ± SD) demonstrated long-term increase in rCBF in the left superior lateral temporal cortex after 45 days of active caprylidene treatment (Scan 3 > Scan 1; $p = 0.04$) in sVOI analyses, that was corroborated by spm: peak voxel [−56, −8, −12], $t = 9.67$, $p < 0.0005$; cluster size = 42 contiguous voxels with $p < 0.01$). In contrast, no significant long-term increase in rCBF was observed for any of the 47 sVOI's in the APOE4-positive subgroup (age 82.2 ± 4.4 yrs., mean ± SD). The spm analyses confirmed the absence of increased activity in the superior temporal gyrus in APOE4-positive subjects, as well as in a number of other areas that spm found to be significantly increased in APOE4-negative, but not in APOE4-positive subjects, including: bilateral anterior cerebellum (peak voxel [−12, −54, −46], $t = 14.82$, $p < 0.0005$; cluster size = 333 voxels, $p = 0.014$ FDR corr.), left inferior temporal cortex (peak voxel [−16, −20, 0], $t = 13.07$, $p < 0.0005$; cluster size = 407 voxels, $p < 0.0005$, $p = 0.008$ FDR corr.) and the right hypothalamus (peak voxel [10, −2, −6], $t = 10.90$, $p < 0.0005$; cluster size = 251 voxels, $p = 0.001$, $p = 0.031$ FDR corr.) (Fig. 2).

No other long-term (Scan 2 vs. Scan 4), or [(Scan 2 - Scan 1) – (Scan 4 - Scan 3)] or acute (Scan 1 vs. Scan 2, Scan 3 vs. Scan 4) changes in rCBF were found to be significant. However, analyses of acute changes in treatment-naïve subjects did suggest an effect of APOE genotype. Generally greater activation associated with caprylidene therapy was observed in APOE4-negative compared to APOE4-positive subjects, particularly apparent in dorsolateral prefrontal and temporal cortices (Fig. 3) when comparing Scan 1 vs Scan 2.

4. Discussion

This randomized, double-blinded study explored the effects of caprylidene treatment over 45 days on regional cerebral blood flow in subjects with mild to moderate AD. We observed an apparent effect of APOE genotype in rCBF response to caprylidene. Increased rCBF was identified in the left superior lateral temporal cortex, and other regions in APOE4-negative, but not APOE4-positive subjects, following caprylidene therapy.

Prior studies have shown cognitive benefits in response to both a single dose and long-term intake of MCTs over several weeks (Reger et al. 2004; Henderson et al. 2009; Krikorian et al. 2012; Newport et al. 2015). The aforementioned studies also identified more pronounced improvements in ADAS-Cog scores in the APOE4-negative, compared to APOE4-positive participants, similar to the observations in rCBF effects here. Equivalent or higher ketone levels appear to be achieved in APOE4-positive individuals, raising the possibility that variability in response by APOE4 status may be attributable to diminished mitochondrial enzyme function in APOE4-positive individuals, preventing adequate utilization of ketone bodies (Reger et al. 2004). Moreover, mitochondrial dysfunction has been suggested to underlie AD pathogenesis, playing a role in beta-amyloid accumulation, excess reactive oxygen species, and cognitive decline (Onyango et al. 2016; Swerdlow et al. 2014)

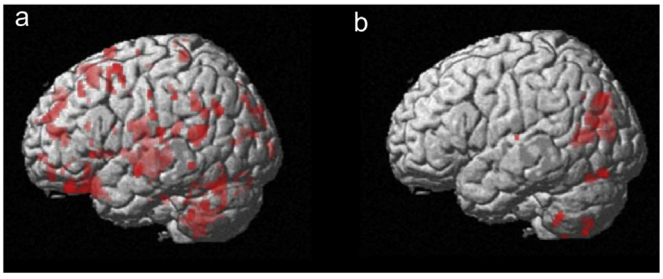

Fig. 2. Long-term effects (Scan 1 vs. Scan 3) of 45 days of daily caprylidene on pre-dose rCBF in APOE4-negative (a) and APOE4-positive (b) groups. Regionally significant increases in cerebral cortex are depicted in the 3D representation of left cerebral hemisphere. Colorscale represents locations of all voxels undergoing increasing activity ($p < 0.01$), and higher density of the redness corresponds to closer proximity to the cortical surface displayed.

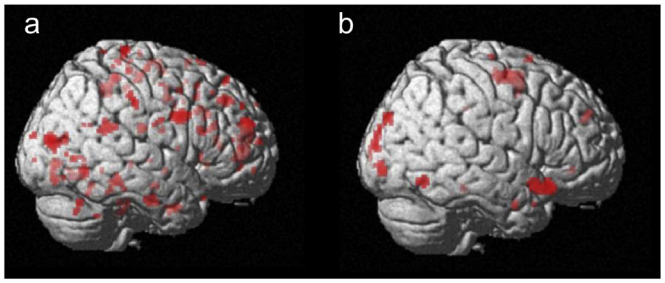

Fig. 3. Acute effects (Scan 1 vs. Scan 2) on treatment-naïve APOE4-negative (a) and APOE4- positive (b) groups. Regionally significant increases in cerebral cortex are depicted in the 3D representation of right cerebral hemisphere. Colorscale represents locations of all voxels undergoing increasing activity ($p < 0.01$), and higher density of the redness corresponds to closer proximity to the cortical surface displayed.

To our knowledge, this is the first study to identify increases in regional cerebral blood flow associated with ketogen administration in patients with AD. Hypometabolism with respect to glucose utilization occurs many years before the onset of AD dementia and correlates with disease progression (Mosconi et al. 2010). There is also evidence that treatment with cholinesterase inhibitors in dementia patients is associated with a significant increase of metabolism in other regions, presumably reflecting responsiveness of more intact functional tissue in those regions (Zaidel et al. 2012). Increases in rCBF noted in APOE4-negative participants in this study also may reflect relatively intact tissue most capable of responding to caprylidene treatment. Indeed, with the exception of temporal cortex, the brain areas reported as being most affected by caprylidene therapy, including cerebellar, subcortical, and frontocortical regions, are known to be relatively spared in mild to moderate AD. The basis for the sensitivity of temporal rCBF to caprylidene is presumably different but as of yet unknown. It may represent increased neuronal function with attendant greater metabolism and increased demand for delivery of energy substrates through increased blood flow (Hertz et al. 2015). Recent studies using FDG and acetoacetate (AcAc) PET in healthy individuals with diet-induced ketosis have aimed to better understand metabolic changes in the brain and show that increased ketone availability raises the cerebral metabolic rate with respect to acetoacetate utilization, but with proportional decreases in the metabolic rate of glucose. It remains to be established whether similar changes occur with aging and dementia (Cunnane et al. 2016).

Many therapeutic interventions in AD have focused on targeting beta-amyloid given its possible role in the progression of AD, but have so far not yielded a disease-modifying therapy with proven efficacy, reaffirming the need to continue to explore other therapeutic strategies (Canter et al. 2016). A ketogenic diet that addresses the brain energy deficit represents one such strategy. Despite regional hypometabolism, ketone uptake remains the same in healthy controls, MCI, and AD, with gradually worsening deficit in glucose utilization occurring before the

onset of significant cognitive changes (Croteau et al. 2018; Cunnane et al. 2016). Ketone supplementation may help delay AD through any of several proposed mechanisms, including improvement in mitochondrial function, reduction in oxidative stress, decrease in amyloid burden, and suppression of neuroinflammation (Augustin et al. 2018; Greco et al. 2016; Hernandez et al. 2017; Shen et al. 2017; Yin et al. 2016).

An obvious limitation of this pilot study is the small number of subjects, which limits its statistical power and generalizability. Another is the small size of the placebo group, which was sufficient as a methodologic tool for maintaining rigorous blinding of subjects ingesting the formulation and investigators analyzing subject-specific data, but not sufficient for carrying out a more conventional active-vs-placebo formulation analysis. Additionally, while participants adhered to daily caprylidene supplementation, the study did not control for the regular diet of these patients, which could potentially affect its findings, though it should be noted that the pivotal trials in the original establishment of clinical benefits for caprylidene did not impose dietary restrictions or changes beyond daily caprylidene supplementation (Henderson et al. 2009; Reger et al. 2004). It should also be noted that the FDR correction applied to the imaging data were intended as a multiple comparison correction for the number of brain elements compared across each pair of conditions analyzed for change in rCBF, and not for the number of pairs of conditions analyzed for change, in this pilot study. Future studies with more subjects and longer periods of treatment may help to further elucidate the neurobiological effects of caprylidene supplementation and identify differential effects on APOE4-positive versus negative participants. Studies comparing exogenous ketone supplements in the setting of non-ketogenic versus ketogenic diets will also be important for better discerning its value. The restrictive nature of a ketogenic diet on its own may pose difficulties with adherence, requiring supplementation with exogenous agents (Cavaleri and Bashar 2018). Finally, the clinical implications of changes in rCBF as a result of caprylidene remain to be determined. Nonetheless, this study serves as a starting point for design of larger randomized controlled trials in the future, to confirm its findings and to clarify the association between rCBF changes and clinical parameters in AD patients.

In conclusion, 45 day caprylidene diet was associated with regionally specific increases in cerebral blood flow in APOE4-negative subjects with AD. These results may point to part of a physiologic mechanism for effects of ketogens in those patients.

Declarations of interest

None.

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