Fatty acids and Glucocerebrosidase activity as potential biomarkers of stearyl-CoA desaturase inhibition; an observational study of inter- and intraday variation in healthy volunteers and patients with Parkinson's disease.

Introduction

Alpha-synuclein (αSyn) plays a major role in Parkinson's disease (PD). Inhibition of stearyl-CoA desaturase (SCD) reduces levels of mono-unsaturated C16 and C18 fatty acids, which are involved in αSyn toxicity. The ratio of unsaturated to saturated fatty acids (fatty acid desaturase index, FA-DI) and GCase activity may be relevant biomarkers for the effects of SCD inhibitors that are being developed for synucleinopathies. However, the inter- and intraday variation in these markers in patients with Parkinson's disease (PWPD) and healthy volunteers (HVs) is unknown.

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Aim

To assess the naturally occurring levels and variation in plasma fatty acids and ceramide metabolism in HVs and PWPD

Methods

- 10 PWPD and 10 age-matched HVs
- Measurement of FA, GCase and GluSph
  - On three consecutive days
  - Throughout the day

Results

- No difference in C16 and C18 FA-DI between PWPD and HVs
- Inter-subject variability per day for C16 FA-DI higher in PWPD (37.7%) compared with HVs (20.7%) , figure 1
  - Comparable for C18 FA-DI
- Inter-day variability for C16 and C18 FA-DI comparable for both HVs and PWPD (table 1)
- GCase in PWPD higher compared to HVs (3.8 µmol/L [0.6 – 7.1]), figure 2

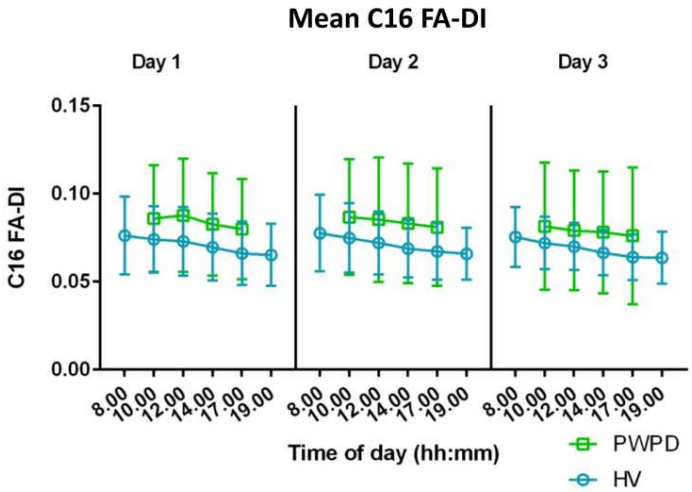

***Figure 1**: Mean and Standard Deviation of Plasma C16 FA DI Time of Day, per Day in Healthy Volunteers and Subjects with Parkinson's Disease*

	C16 FA-DI %CV HV	C16 FA-DI %CV PWPD	C18 FA-DI %CV HV	C18 FA-DI %CV PWPD
Day 1	27.12	35.65	18.63	19.00
Day 2	24.9	40.35	16.22	17.05
Day 3	20.87	45.70	19.28	12.88

Table 1: Mean inter-day variability for C16 and C18 FA-DI in HV and PWPD

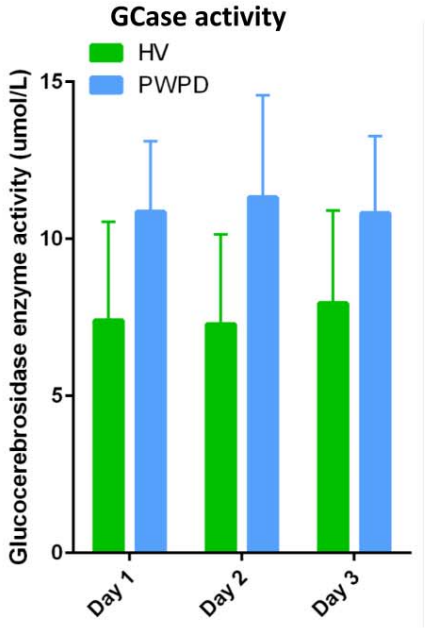

Figure 2: Mean and Standard Deviation of Glucocerebrosidase (GCase) Activity per Day in Healthy Volunteers and Subjects with Parkinson's Disease

Conclusions

- C16 and C18 FA-DI suitable biomarkers for SCD target inhibition due to low inter- and intra-day variability
- Observed GCase difference not in line with previous reports (higher in HVs)
  - Small sample size
  - Heterogenous cell population

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