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Effects of meal timing on human plasma metabolite rhythms

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The term 'chrono-nutrition' describes the interaction between circadian timing and nutritional intake, as demonstrated by a wealth of animal and human studies[(1)]. This relationship is bidirectional, with post-prandial response varying across the day and meal timing acting as a synchronising signal for some circadian rhythms. In humans, we have demonstrated that meal timing is a strong synchroniser of plasma glucose rhythms[(2)]. Our recent data also suggest that interstitial glucose concentration can anticipate large meals[(3)]. However, little is known about the effects of meal timing on other metabolic pathways. The existence of circadian rhythms in human plasma metabolites[(4-6)] provides a clear opportunity to address this timely issue. Here, in a controlled laboratory protocol, we tested the hypothesis that the anticipation of large meals is observed in human plasma metabolites.

Twenty-four male participants undertook an 8-day laboratory study, with strict sleep-wake schedules, light-dark schedules, and food intake. For 6 days, participants consumed either hourly small meals throughout the waking period or two large daily meals (7.5 and 14.5 h after wake-up). Isocaloric meals were calculated using the Mifflin St Jeor formula, and contained 55% carbohydrate, 15% protein, 30% fat[(2)]. All participants then undertook a 37-h constant routine. Samples were collected across a 30-h period in the middle of the constant routine. Plasma was collected every 30 minutes for targeted UPLC-MS/MS metabolomics analysis (Absolute p180 Biocrates kit), and saliva was collected hourly for assessment of melatonin onset, a marker of circadian timing. Data were statistically evaluated by cosinor analysis, unpaired t-test, and repeated measures ANOVA.

There was no difference ($p > 0.05$) in melatonin onset between the two groups. Rhythms, as indicated by significant ($p < 0.05$) cosinor fit, were detected in 64 plasma metabolites (out of 141 detected) in both groups. These metabolites included glucose, triglyceride, cholesterol, plus multiple amino acids, acylcarnitines, phospholipids and sphingolipids. Consistent with previous work, there was a large (c. 7-hour) difference in the phase of plasma glucose between groups, with no significant difference in the phase of plasma triglyceride. Some other metabolites (e.g. histidine and proline) exhibited phase changes like that of glucose, but the phase was mostly unchanged. Glucose, alanine, arginine, citrulline, glutamine, methionine, phenylalanine, met-SO, 3 acylcarnitines and 13 phospholipids exhibited a significant interaction (FDR <0.05 meal-size x time, n=25). Totalcholesterol, asparagine, glutamate, glycine, isoleucine, leucine, ornithine, proline, serine, threonine, tryptophan, tyrosine, kynurenine, SDMA, sarcosine, t4-OH-Pro, taurine, 6 acylcarnitines, 25 phospholipids and SMC18:1 exhibited a significant effect of meal-size and time. A further 8 metabolites had a significant effect of time only. Sixteen metabolites had no significant differences in neither meal size nor time. Our data therefore reveal novel effects of meal timing on multiple metabolite rhythms and average daily concentrations.

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