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Original article

Investigating the effects of an oral fructose challenge on hepatic ATP reserves in healthy volunteers: A ^{31}P MRS study☆

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SUMMARY

Background: Impaired homeostasis of hepatic ATP has been associated with NAFLD. An intravenous fructose infusion has been shown to be an effective challenge to monitor the depletion and subsequent recovery of hepatic ATP reserves using ^{31}P MRS.

Aims: The purpose of this study was to evaluate the effects of an oral rather than intravenous fructose challenge on hepatic ATP reserves in healthy subjects.

Methods: Self-reported healthy males were recruited. Following an overnight fast, baseline liver glycogen and lipid levels were measured using Magnetic Resonance Spectroscopy (MRS). Immediately after consuming a 500 ml 75 g fructose drink (1275 kJ) subjects were scanned continuously for 90 min to acquire dynamic ^{31}P MRS measurements of liver ATP reserves.

Results: A significant effect on ATP reserves was observed across the time course ($P < 0.05$). Mean ATP levels reached a minimum at 50 min which was markedly lower than baseline (80 ± 17% baseline, $P < 0.05$). Subsequently, mean values tended to rise but did not reach statistical significance above minimum. The time to minimum ATP levels across subjects was negatively correlated with BMI ($R^2 = 0.74$, $P < 0.005$). Rates of ATP recovery were not significantly correlated with BMI or liver fat levels, but were negatively correlated with baseline glycogen levels ($R^2 = 0.7$, $P < 0.05$).

Conclusions: Depletion of ATP reserves can be measured non-invasively following an oral fructose challenge using ^{31}P MRS. BMI is the best predictor of postprandial ATP homeostasis following fructose consumption.

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1. Introduction

Both NAFLD and non-alcoholic steatohepatitis (NASH) have been associated with impaired homeostasis of hepatic adenosine triphosphate (ATP) levels [1] and baseline hepatic ATP reserves have been shown to be more depleted in obese subjects [2,3]. It is widely accepted that the inhibition of AMP-activate protein kinase (AMPK) which stimulates ATP synthesis is an important part of liver lipid accumulation [4,5] and it has also been suggested that an inability to maintain ATP levels may prime hepatocytes to become vulnerable to injury by reactive oxygen species.

Hepatic ATP reserves can be monitored noninvasively using ^{31}P magnetic resonance spectroscopy (MRS) [6]. Early animal studies used this method to monitor ATP following fructose injections and

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; ATP, adenosine triphosphate; MRS, magnetic resonance spectroscopy; Pi, inorganic phosphate; PDE, phosphodiesters; PME, phosphomonoesters; IV, intravenous; ISIS, image selective *in vivo* spectroscopy; NOE, nuclear overhouser effect; SD, standard deviation; ADP, adenosine diphosphate; AMP, adenosine monophosphate; AMPK, amp-activated protein kinase; UTP, uridine triphosphate.

☆ **Department and institution of study**: All work was conducted at the Sir Peter Mansfield Imaging Centre in the University of Nottingham, UK.

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suggested its potential use as a diagnostic method for studying liver disease [7]. A number of more recent studies have used these techniques to measure ATP homeostasis following an intravenous (IV) fructose load [2,8,9]. Fructose infusion causes the depletion of hepatic ATP levels due to a lack of phosphorylation feedback which results in continued phosphorylation activating AMP deaminase and uric acid production (supplementary material) [10]. During these studies, subjects undergo continuous ^{31}P MRS immediately following a fructose bolus injection to measure minimum ATP levels and subsequent rates of replenishment.

The effects of fructose consumption on liver lipids [11] and NASH [12] have been considered in the literature, but little research has investigated the immediate ATP response to an oral fructose challenge. The present study investigated postprandial changes to hepatic ATP reserves following an oral fructose intake.

2. Material and methods

2.1. Subjects

All subjects were self-reported healthy non-obese males with sedentary lifestyles and no known metabolic disorders. All subjects consumed the oral challenge in the time required (5 min) and complied well with the lifestyle restrictions and scanning requirements. The mean age for all subjects was 24 ± 4 years and BMI was 25 ± 3 kg/m^2.

2.2. Study design

2.2.1. Ethical permission

Ethical permission was obtained from the local Medical School Research Ethics Committee and subjects provided written informed consent before participation.

2.2.2. Subjects

At the time of this investigation there were no published data on ^{31}P MRS ATP following an oral fructose challenge which could be used to estimate the power of the study. We therefore chose a sample size for this first exploratory study based on data reported in infusion studies [[13], n = 8].

Prior to study days subjects were asked to refrain from alcohol for 24 h. On the morning of the study subjects arrived at the test centre between 7:30am and 8:00am having fasted overnight.

On arrival, natural abundance ^{13}C MR spectra were acquired from the liver to determine baseline hepatic glycogen levels, and localized ^{1}H MR spectra were acquired to determine baseline hepatic lipid levels. Subjects were then asked to consume a 500 ml drink of 75 g fructose solution (1275 kJ) within 5 min. Immediately following consumption, subjects were placed in the scanner and ^{31}P MR spectra were acquired continuously for 90 min to assess dynamic changes in ATP and related phosphate metabolites. During the 90 min of scanning, subjects were asked to breathe regularly and remain as still as possible and were allowed to listen to the radio or music.

2.3. Data acquisition

All measurements were performed on a Philips Achieva 3T system (Philips, Best, The Netherlands) using the built-in ^{1}H transmit/receive body coil for scout images and voxel placement.

2.3.1. ATP

Dynamic changes in phosphate metabolites were measured using localized ^{31}P MRS. A ^{31}P surface coil (Philips, Best, The Netherlands) was placed on the abdomen over the liver. Scout ^{1}H images were obtained and used for voxel placement in the right lobe of the liver (60 × 60 × 60 mm^3 voxel size). ^{31}P spectra were obtained continuously for 90 min using a respiratory triggered ISIS sequence with Nuclear Overhouser Effect (NOE) enhancement and proton decoupling (3 kHz bandwidth, 2048 samples, 5000 ms repetition time) as described previously [14,15]. The voxel for β-ATP was positioned against the abdominal wall with the chemical shift of all other metabolites directed away from the wall to minimize signal leakage from the abdominal muscle (confirmed by a lack of spectral PCr peak) and maximize signal for β-ATP.

2.3.2. Hepatic lipids

Baseline lipid levels were measured using the integrated ^{1}H body coil. Scout images were obtained and used for voxel placement (30 × 30 × 30 mm^3 voxel size). ^{1}H spectra were obtained using a respiratory triggered, water suppressed STEAM sequence (2 kHz bandwidth, 1024 samples, 13 ms echo time, 5000 ms repetition time, 40 averages). Two spectra were collected without water suppression for correction to absolute lipid fat fractions as described previously [15].

2.3.3. Glycogen

Baseline glycogen levels were measured using unlocalized ^{13}C MRS. A surface coil with integrated quadrature proton decoupling (PulseTeq, Surrey, UK) was placed on the abdomen over the liver. Scout ^{1}H images were used to determine correct placement. ^{13}C spectra were obtained using a $\pi/2$ pulse-acquire sequence with an adiabatic half passage pulse shape to minimize the effects of B_1 field inhomogeneity within the volume of interest, along with narrow band proton decoupling (7 kHz bandwidth, 512 samples, 2150 ms repetition time, 576 averages, ~20 min total acquisition time) as previously described [16].

2.4. MRS analysis

2.4.1. ATP

^{31}P spectra were line broadening by 30 Hz and data were averaged over 15 min windows at 5 min intervals across the time-course. The β-ATP peak position was defined in the spectra and peak area calculated across the time course (Fig. 1). The β-ATP peak provides a way of measuring total ATP because the phosphate signal from ADP overlaps with the α-ATP and γ-ATP peaks. The first time point was taken as a reference to measure changes in ATP and recorded as % of baseline value.

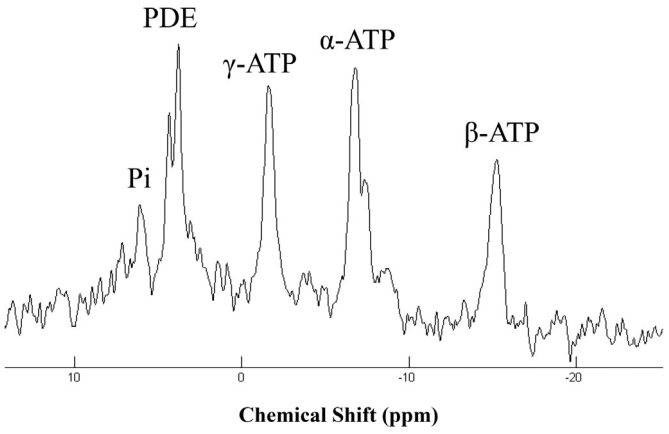

Fig. 1. 31P Magnetic Resonance Spectrum from one subjects showing signal peaks from ATP (β-ATP, α-ATP and γ-ATP), phosphodiesters (PDE) and inorganic phosphate (Pi).

Time to reach minimum ATP levels was calculated, and the rate of recovery of absolute ATP was determined using the gradient across the first 4 time points of recovery using linear fitting. For recovery rates, ratios of β-ATP to total phosphorous levels were taken as used in previous studies [3].

2.4.2. Hepatic lipids

^{1}H spectra were zero filled to 1024 datapoints and phase corrected before peak areas were calculated using the AMARES algorithm in jMRUI (Universiteit Leuven, Belgium) [17] (Lorentzian curve fitting of water peak at ~4.8 ppm and -$[CH_2]_n$-at ~1.3 ppm). Water suppression was applied during spectral acquisition for better resolution of the fat peak, followed by unsuppressed spectra with identical parameters to determine the water peak area. Peak areas were corrected for T_2 relaxation as determined from previous studies and lipid/water ratios used to determine absolute fat fractions as described by Stephenson et al. [23].

2.4.3. Glycogen

^{13}C spectra were zero filled to 4096 datapoints and 100 Hz line broadening was applied before Lorentzian curve fitting using in house software. Integrals of the C1-glycogen peak (100.4 ppm) and of an external reference peak were measured and ratios used to account for varying loading factors. Quantification was achieved by comparing glycogen/reference ratios with a phantom [18].

2.5. Statistical analysis

All results are expressed as means (±SD). A repeated measures ANOVA F-test was used to determine a significant effect across the time course, and a means difference T-tests were subsequently used on individual time points to determine significant changes. Significances in correlations were determined using linear regression analysis with Pearson correlation coefficients quoted. In all cases significance was attributed to $P < 0.05$. The statistical package used for analysis was SPSS version 21 for Windows (SPSS, Inc., Chicago, IL).

3. Results

3.0.1. Baseline hepatic lipid and glycogen

The mean baseline liver lipid fat fraction was 4 ± 3% and correlated significantly with BMI ($R^2 = 0.48$, $P \leq 0.05$) as expected.

The mean baseline hepatic glycogen concentration was 219 ± 81 mmol/l and there were no correlations between individual values and age, BMI or baseline liver lipid levels.

3.0.2. ATP reserves following oral fructose challenge

Mean postprandial hepatic ATP levels began to decline from 15 min after the oral fructose challenge (Fig. 2). A statistically significant variation from baseline was found across the time course (One way ANOVA F-test, $P < 0.05$). Mean values continued to decline and were significantly below the first two points at t = 30 min (86 ± 14%, $P < 0.05$), t = 40 min (85 ± 16%. $P < 0.05$) and t = 45 min (84 ± 14%, $P < 0.005$) until reaching minimum at = 50 min (80 ± 17%, $P < 0.05$). There was a trend for values to recover after 50 min, but the increase was not statistical significance compared to nadir and levels remained lower than baseline at the end of the study.

No subject showed any recovery of ATP levels during the first 6 time points (until t = 40 min). The mean AUC across this period (t = 0 to t = 40 min) was 232 ± 19% h and showed a strong negative correlation with BMI ($R^2 = 0.65$, $P < 0.01$).

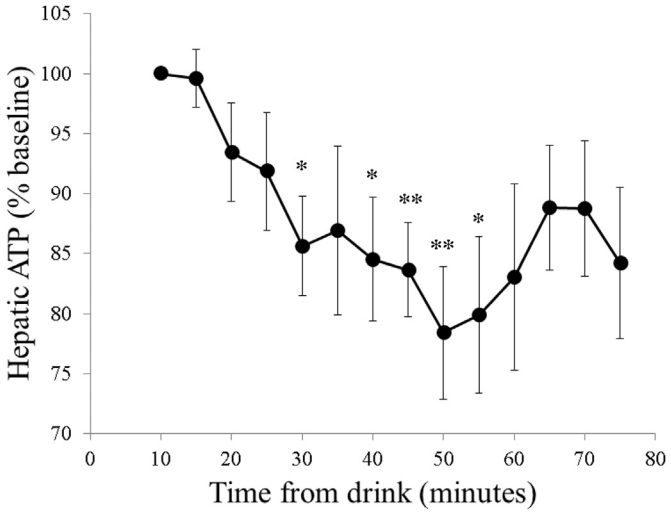

Fig. 2. Changes in Hepatic ATP (β-ATP peak) from baseline in response to a 75 g oral fructose challenge measured using 31P MRS (n = 9). *P < 0.05, **P < 0.01.

3.0.3. Time to minimum ATP

For two subjects the minimum ATP time point was at the end of the scanning period, and as such the final time point was taken as their time to minimum ATP (which may in fact have been after the scan period). A significant negative correlation was found between time to minimum ATP and BMI ($R^2 = 0.74$, $P < 0.005$) as shown in Fig. 3. No such correlation was observed with age ($R^2 = 0.01$, $P = 0.78$) or baseline glycogen ($R^2 = 0.003$, $P = 0.88$) but the correlation approached significance with baseline liver fat ($R^2 = 0.39$, $P = 0.07$).

3.0.4. Rate of recovery

Figure 4 shows the relationship between rate of recovery and baseline glycogen reserves, which had a strong negative correlation that was statistically significant ($R^2 = 0.71$, $P < 0.05$). This correlation was not observed with BMI, liver fat, or any other baseline measures.

4. Discussion

The underlying physiological hypothesis of this study is that ATP homeostasis, which provides a measure of AMPK activity, acts as a

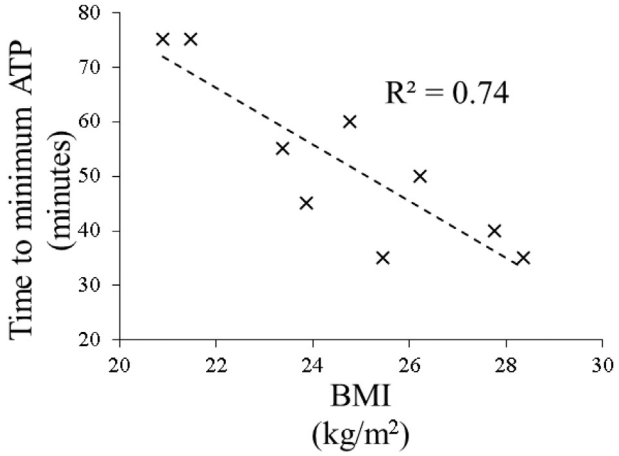

Fig. 3. Correlation between time to minimum ATP (β-ATP peak) and BMI ($P < 0.005$).

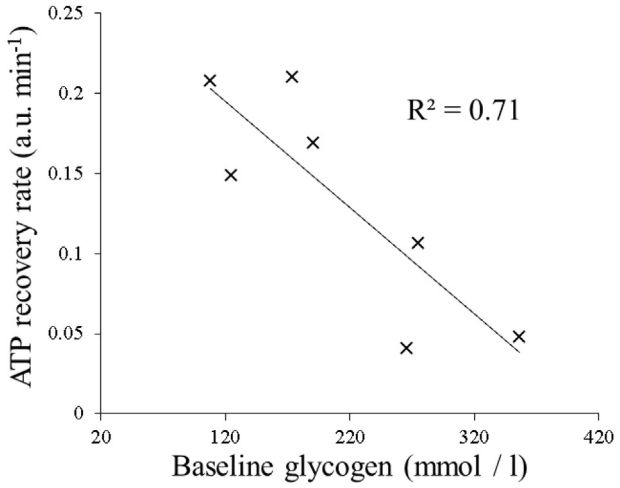

Fig. 4. Correlation between rate of ATP recovery (β-ATP peak) and baseline glycogen levels measured using 31P MRS ($P < 0.05$). Recovery rate is measured as the gradient of [β-ATP signal/total phosphorous signal] across the first four points of recovery.

biomarker for NAFLD and NASH. Rather than fructose infusion, this study explored using ^{31}P MRS following an *oral* fructose challenge, which is more physiological, more patient-acceptable and much simpler to administer. The results showed that after oral consumption there is a measurable decline in ATP reserves (β-ATP) followed by a partial recovery. This observation is characteristic of fructose metabolism and can be explained as a result of the immediate rapid phosphorylation of the monosaccharide. Under normal physiological conditions an increased cellular level of adenosine monophosphate (AMP) activates AMPK resulting in the regeneration of ATP, whereas under conditions where AMPK activity is lower (e.g. following fructose consumption) the production of uric acid is favoured over ATP (supplementary material). In addition to this, fructose has been shown to up-regulate Glut5 and Fructokinase [19], and subjects with NAFLD and a higher intake of fructose have been shown to have a greater hepatic mRNA expression of fructokinase [20].

In a small study of 4 subjects Buemann et al. tested the effects of an oral dose of 30 g D-Fructose and D-Tagatose on hepatic ATP reserves at 1.5T [21] and reported no drop in ATP following D-fructose consumption (however, they did find a drop following D-Tagatose which reached a maximum at 51 min). The data from the present study suggests that a greater concentration of fructose and high resolution spectra (3T scanner) may be required to observe significant reductions.

In the present study ATP levels took longer to recover compared to previous infusion studies. This is probably due to the extra stages necessary to transfer fructose to the hepatic tissue, namely gastric emptying and intestinal absorption. Gastric emptying has been shown to be dependent on meal energy and volume [22], which becomes relevant to the techniques used here when considering the optimum energy content and volume of the fructose challenge to induce sufficient depletion of hepatic ATP. Another confounding factor is the variation in fructose intestinal absorption rates reported in the literature. A previous study showed a high variability in intestinal absorption of fructose in healthy subjects following an oral fructose drink [23]. The amount of fructose used in the present study was sufficient for intestinal absorption and delivery to the liver in all subjects, but this factor should be considered in future experiments, and it may be that lower doses and volumes of fructose will not have the same effect.

This study showed a negative correlation between BMI and time to minimum ATP levels. Given that the hepatic ATP response is a combination of depletion and recovery and fructose is known to deplete ATP reserves, these findings suggest that individuals with lower BMI have a more effective hepatic ATP recovery in response to a high fructose challenge. This result may be confounded by changes in gastrointestinal function, but also confirms previous studies that have shown that obese subjects have an impaired efficiency of ATP replenishment [2]. Surprisingly this correlation was not observed with liver fat levels as might be expected. Previous studies have shown that there is an impaired hepatic ATP homeostasis in Type 2 diabetes [24] and it has been suggested that this may precede the development of steatosis in these patients [3]. Whether or not there is a causal link between rates of ATP synthesis and metabolic disorders remains to be established. Related to this, it has been suggested that regular consumption of fructose upregulates fructokinase and that this may be a factor in NAFLD development and the high incident rates observed currently [20]. In the present study we did not acquire a full dietary history, but future studies in this area should explore the effects of prior exposure and its relevance to ATP depletion and recovery rates and steatosis.

This experiment required 2 h of scanning on a high field MRI scanner, which may be impractical and costly in a clinical setting. However, it is possible that other related measures may provide a more convenient marker. For example, there was a significant negative correlation between the AUC over the first 6 time points and BMI. These measures can be made over a shorter scan duration. Future studies should consider a wider range of liver fat, as well as NAFLD and NASH patients. In particular, studies that separate BMI from liver fat to determine which of these is a better predictor of ATP homeostasis, although admittedly it would be difficult to recruit for this given the correlation between BMI and liver fat.

Baseline glycogen measurements gave a wide range of values, which suggests variability in the timing and content of the previous evening meal across subjects [16]. Whilst this may reveal a potential limitation in the study design, the results showed for the first time a significant negative correlation between rates of ATP synthesis and baseline glycogen levels which may be relevant to patients with glycogen storage disease and other metabolic disorders. Previous studies have shown that a fructose load activates glycogen synthase resulting in increased glycogenesis, and also that fructose-1-phosphate produced during fructose metabolism is a competitive inhibitor of phosphorylase *a* [25] resulting in a slowed glycogenolysis. These factors result in an increase in glycogen synthesis following fructose consumption. The relationship between glycogen levels and ATP reserves has been explored in a number of publications and correlations between glycogen synthesis and ATP turnover in muscle [26] and between absolute hepatic glycogen levels and total hepatic ATP content during glycogen repletion [27] have been reported. This has been explained as the need for increased uridine triphosphate (UTP) during periods when unidirectional flux of glycogen synthesis is greater than glycogenolysis, which results in greater ATP synthesis. A possible explanation for the negative correlations between rates of ATP synthesis and baseline glycogen levels observed in the present study is that there is a greater demand from hepatic glycogen in subjects with lower baseline glycogen levels, resulting in an increased rate of glycogen synthesis and indirectly ATP synthesis. Whilst it is beyond the scope of this study to determine this causal link, this study shows that baseline hepatic glycogen levels are an important factor in the ATP response to fructose.

The present study has some limitations. Firstly, breath samples were not obtained to estimate levels of intestinal fructose malabsorption [28]. Measuring changes in serum uric acid would also be ideal as hyperuricemia has been associated with an impaired hepatic ATP homeostasis in response to high fructose intake [3].

Future experiments should obtain blood samples to measure this also. Secondly, histological comparisons were not made due to the ethical considerations of liver biopsies in healthy subjects. As such, although all subjects in this study had no known liver health problems this was not confirmed through histological analysis. Other studies should investigate the postprandial ATP effects in patients with NASH in comparison with healthy weight and obese people, as well as individuals with Type 2 diabetes. Similarly, all subjects in this study were healthy non-obese male volunteers and it should be acknowledged that the response may be different in women or an obese cohort. Subjects also found 500 ml fluid difficult to consume and the scan time was long and potentially uncomfortable. Future studies should optimize the experimental protocol, in particular the time duration, time resolution and volume or concentration of fructose challenge used.

In summary, this study has shown that depletion in hepatic ATP reserves following an oral fructose challenge is observable using ^{31}P MRS in healthy subjects, allowing for a completely non-invasive assessment of ATP synthesis. BMI was negatively correlated with the time to minimum ATP levels and with ATP levels immediately post consumption indicating an impaired hepatic energy homeostasis in subjects with higher BMI.

Conflict of interest

The first author is part of an industrial collaborative award in science and engineering (CASE) studentship funded jointly by the Biotechnology and Biological Sciences Research Council (BBRSC) and Unilever.

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Authors contributions

Study conception and design: SB; MS; LM; GA; PM; PG.
Acquisition of data: SB; MS.
Analysis and interpretation of data: SB; MS; GA; IM; LM; PG.
Drafting of manuscript: SB.
Critical revision: SB; MS; EC; KH; LM; IM; GA; PM; PG.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2015.04.001.

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