Journal of Food Research; Vol. 8, No. 5; 2019
ISSN 1927-0887 E-ISSN 1927-0895
Published by Canadian Center of Science and Education

Effects of Oligofructose-enriched Inulin and Digestive Symptoms on Subjective Wellbeing, Mood and Cognitive Performance

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Received: June 7, 2019 Accepted: July 3, 2019 Online Published: July 26, 2019

doi:10.5539/jfr.v8n5p33 URL: https://doi.org/10.5539/jfr.v8n5p33

Abstract

Rationale: Research has shown that the behavioural effects of inulin vary depending on dose, whether combined with food or not, and length of time that the inulin is consumed.

Objectives: The aim of this study was to examine the acute effects of 13g of inulin on digestive symptoms, mood and cognitive performance.

Methods: This study compared 13g of inulin and maltodextrin placebo over a single day using a cross-over design (N=51), with a measurement of mood and cognition occurring across the day.

Results: Inulin increased the number of motions occurring and the number of stools passed. Inulin was associated with a more negative mood and impaired cognition, especially episodic memory.

Conclusions: Inulin can influence behaviour through a variety of mechanisms. Effects seen in this study could not reflect changes in gut flora due to the short time period studied. Other possible mechanisms are discussed.

Keywords: alertness, cognition, digestive problems, inulin, memory, mood, oligofructose-enriched inulin, wellbeing

1. Introduction

The starting point for the present research was a study investigating the effects of high fibre breakfast cereal on mental energy (Smith et al., 2010a). Correlational data from the baseline assessments showed that regular consumption of high fibre cereals was associated with reduced fatigue. A 14 day intervention study confirmed that consumption of high fibre breakfast cereal was associated with increased energy compared to the placebo group. The initial interpretation of these results was in terms of the fibre improving digestive functioning. Smith (2010a, 2011) conducted secondary analyses of a large epidemiological database (Smith et al., 2000) and found that digestive symptoms had a negative impact on wellbeing. This finding confirms results showing impaired cognition in patients with irritable bowel syndrome (Berrill et al., 2013; Kennedy et al., 2014). However, the beneficial effects of a high fibre diet did not only reflect the reduction in digestive problems (Smith, 2010). This led to consideration of other underlying mechanisms and one possibility was that wheat bran has a prebiotic effect (stimulates beneficial bacteria in the colon) which could lead to beneficial behavioural changes. The hypothesis that wheat bran stimulates beneficial bacteria in the colon has been shown to be incorrect (Smith, Deaville and Gibson 2018) but it led to consideration of established prebiotics such as inulin.

Inulin is found in many plants that are part of the human diet (e.g. leeks, onions, wheat, garlic, chicory and artichokes). It is added to many foods to increase dietary fibre, replace fats or carbohydrates, and as a prebiotic (Gibson et al., 1995; Roberfroid, 2007). Inulin is usually combined with a similar compound, oligofructose, and most published research has used this combination. Inulin has been widely studied (a pubmed search reveals over 10,000 articles) but there have been few studies of its behavioural effects. In a similar study to the wheat bran research described above, Smith (2005) conducted a 14 day intervention study using 10g of oligofructose-enriched inulin and maltodextrin placebo. As well as questionnaires measuring wellbeing the study also included mood ratings and cognitive tasks. The results showed that inulin did not improve well-being, mood, or performance but led to an increase in digestive problems (wind, feeling bloated and stomach cramps). It was suggested that any beneficial prebiotic effects may have been negated by the increased digestive problems.

Animal research (Messaoudi et al., 2005) suggests that ingestion of inulin may lead to improved cognition. This study used oligofructose-enriched inulin at doses of 5 and 10 % in the diet, orally ingested daily for 2 weeks. Control rats received a standard diet and were tested in the same test situations. The behavioural effects were investigated after the administration period by lever-pressing activity and learning discrimination using the light extinction paradigm. The results showed that oligofructose-enriched inulin, and particularly at 10 % in the diet, increased the general activity of the rats and their learning discrimination. The high doses used in this study would not be ingested by humans and most research with humans has used doses of less than 15g due to the increase in digestive symptoms with high doses.

Smith et al. (2015) investigated the acute effects of 5g inulin combined with food and demonstrated beneficial effects on digestion, mood and memory over a 4 hour period. The first study described in this article continued examining the acute effects of inulin (Orafti®Synergy1) and used a larger dose over a longer time period. Oligofructose-enriched inulin (Orafti®Synergy1) is a combination of chicory-derived inulin with selected chain lengths, enriched by a specific fraction of oligofructose, produced by partial hydrolysis of chicory inulin in an about 50/50 ratio. The animal research suggested that larger doses of inulin may have larger effects and this was examined here by investigating effects of 13g oligofructose-enriched inulin over a 12 hour period using a sample of university students. The outcome measures in the first study were based on those used by Smith (2015), namely mood and cognitive function.

2. Methods

The study was approved by the ethics committee, School of Psychology, Cardiff University, and carried out with the informed consent of the volunteers.

2.1 Design

A cross-over design was used with half the participants having the inulin (Orafti® Synergy1) on the first visit and the placebo (maltodextrin) on the second (with at least one clear day between visits), and the other half having the placebo and inulin conditions in reverse order. On test days, participants reported to the laboratory at 08:00 and completed a baseline battery of computerised mood and performance tests. They were given breakfast at 09:00, which consisted of yoghurt containing 8g of inulin or placebo. During the morning the participants completed questionnaires relating to how they had recently been feeling over the past 7 days and were allowed to read when they had completed these. The next test session was at 11:00, followed by lunch (a sandwich based meal; approximately 539 kcal; 20.7g fat, 65.5g carbohydrate and 22.7 g protein) and another 5g of inulin or placebo given in decaffeinated tea, decaffeinated coffee, or fruit juice at 12:00. The second inulin dose was reduced to 5g as digestive side effects (e.g. diarrhoea) had been observed with doses greater than 15g per day. Three more test sessions were completed at 14:00, 16:30, and 19:00 (see Table 1).

Table 1. Schedule of testing – Study 1

08:00	Baseline measures taken
09:00	Breakfast (yoghurt with or without 8g inulin/placebo) + decaffeinated tea/coffee
10:00	Pre-test questionnaires (past 7 days)
11:00	Morning test session
12:00	Lunch (sandwiches) + decaffeinated tea/coffee with or without 5g inulin/placebo
14:00	First afternoon test session
15:00	Decaffeinated tea/coffee
16:30	Second afternoon test session
17:30	Decaffeinated tea/coffee
19:00	Final test session
20:00	Post-test daily diary completed

2.2 Participants

Volunteers for the study were screened prior to inclusion and they were excluded if (1) there was an existing disease or participants were receiving medication, (2) if they were heavy smokers (>10 cigarettes a day), (3) if alcohol consumption was high (females > 20 units a week; males > 30 units a week), and (4) if they were high fibre consumers (above 3rd quartile, as measured by a fibre questionnaire – see supplementary material). In total, 53 participants were recruited; however, 2 of these withdrew from the study. The final sample consisted of 12 males and 39 females (mean age 22 years, age range 19-54 years).

2.3 Measures

Volunteers completed a battery of questionnaires assessing their fatigue/energy, subjective mood, physical and mental health, bowel function and fibre intake over the week prior to the test day (see supplementary material). At the end of each test day, volunteers completed a daily diary asking about their wellbeing and digestive functioning. At each test session (08:00, 11:00, 14:00, 16:30, and 19:00), volunteers completed the performance tests and mood ratings based on those used in Smith et al. (2015) which are described in detail in the supplementary material. The outcomes analysed were:

- Daily evacuation of bowels
- Mood – alertness, hedonic tone and anxiety
- Episodic memory – immediate recall of a list of 20 words; delayed recall; recognition memory
- Logical reasoning
- Semantic processing
- Simple reaction time
- Lapses of attention (long responses in a choice reaction time task)
- Cognitive vigilance hits and reaction time

These measures were selected because they reflect a range of different behavioural functions and were also used in Smith et al. (2015).

2.4 Statistical Analysis

2.4.1 Study 1 (Acute Effects)

These largely involved analyses of co-variance. The first factors to be entered into the model were the baseline measures, which were used as covariates. These were followed by inulin/placebo conditions, order of conditions, and then the interactions of all these variables. Separate analyses were carried out for the morning and afternoon sessions. These analyses determined whether there was a global effect of inulin, whether effects were task specific, and if effects persisted over time. A correction was used for the number of analyses conducted using the Holm-Bonferroni method (Holm 1979).

3. Results

3.1 Daily Record of the Evacuation of Bowels

There was a significant main effect of inulin on the number of motions (F (d.f. 1,48)=6.75, p<0.012), with a rise in the number of motions after being given inulin (Placebo – mean=0.58, s.e.=0.10; Inulin – mean=0.96, s.e.=0.14). There was a significant main effect of inulin on the number of stools passed (F(1,40)=4.53, p<0.040), with a rise in the number of stools passed after being given inulin (Placebo – mean=1.02, s.e.=0.23; Inulin – mean=1.71, s.e.=0.26).

3.2 Mood and Performance in the Morning

The mood results are shown in Table 2. This shows means, standard errors, level of significance (p-value) and level of significance adjusted for the number of analyses conducted (Holm-Bonferroni p-value).

Table 2. Mood ratings given after inulin and placebo (scores are the adjusted means; higher scores = more positive mood)

Variable	Inulin mean (se)	Placebo mean (se)	p value	Holm-Bonferroni Corrected p value
Alertness	192.5 (6.8)	206.6 (6.7)	0.022	0.044
Hedonic Tone	166 (4.2)	174.0 (3.4)	0.009	0.018
Anxiety	90.7 (1.7)	89.2 (1.7)	0.67	0.67

There was a significant main effect of inulin on ratings of alertness (F(1,48)=5.60, p<0.022), with ratings in the inulin condition being significantly below those in the placebo condition. Hedonic tone is a measure of how pleasant or happy a person is feeling. There was a significant main effect of inulin on ratings of hedonic tone (F(1,48)=7.52, p<0.009), with ratings in the inulin condition being significantly below those in the placebo condition. Both of these effects remained significant after a Holm-Bonferroni correction. There was no significant effect of inulin on anxiety.

The performance task results are shown in Table 3.

Table 3. Performance scores after inulin and placebo (scores are the adjusted means)

Variable	Inulin mean (se)	Placebo mean (se)	p value	Holm-Bonferroni corrected p value
Immediate recall (number correct)	9.4 (0.4)	11.0 (0.5)	0.002	0.018
Delayed recall (number correct)	5.9 (0.5)	7.3 (0.5)	0.002	0.018
Recognition memory hits	13.8 (0.6)	15.3 (0.5)	0.005	0.035
Semantic processing (number correct)	66.9 (1.4)	69.4 (1.5)	0.005	0.035
Logical reasoning (number correct)	87.3 (1.0)	89.2 (1.0)	0.015	0.075
Sustained attention hit RT (msec)	750 (14.9)	722 (13.4)	0.028	0.112
Sustained attention hits	17.2 (0.6)	17.8 (0.6)	0.038	0.114
Number of lapses	6.0 (0.7)	4.4 (0.9)	0.183	0.366
Simple RT (msec)	343 (5.0)	344 (5.2)	0.419	0.419

3.3 Memory Tasks

3.3.1 Immediate Recall: Number of Words Recalled Correctly

There was a significant main effect of inulin on the number of words recalled correctly ($F(1,48)=11.18$, $p<0.002$), with fewer words recalled correctly after inulin compared to the placebo condition.

3.3.2 Delayed Recall: Number of Words Recalled Correctly

There was a significant main effect of inulin on the number of words recalled correctly ($F(1,48)=11.37$, $p<0.002$), with fewer words recalled correctly after inulin compared to the placebo condition.

3.3.3 Delayed Recognition Memory: Number of Targets Correctly Recognised

There was a significant main effect of inulin on the number of targets recognised correctly ($F(1,48)=8.87$, $p<0.005$), with fewer correct responses occurring after inulin compared to the placebo condition.

3.3.4 Semantic Processing: Number of Trials Correct

There was a significant main effect of inulin on the number of trials correct ($F(1,48)=8.78$, $p<0.005$), with fewer correct trials occurring after inulin compared to the placebo condition.

All of the above effects remained significant after a Holm-Bonferroni correction was applied.

3.3.5 Logical Reasoning: Number of Trials Correct

There was a significant main effect of inulin on the number of trials correct ($F(1,48)=4.45$, $p<0.040$), with fewer correct trials occurring after inulin compared to the placebo condition. This effect was no longer significant after a Holm-Bonferroni correction was applied.

3.4 Psychomotor Tasks

There were no significant effects of inulin on the simple RT task and the number of lapses in the choice reaction time task.

3.5 Sustained Attention Task

3.5.1 Repeated Digits: Total Hits

There was a significant main effect of inulin on the number of hits ($F(1,48)=4.55$, $p<0.038$), with fewer hits occurring after inulin compared to the placebo condition. This was no longer significant after a Holm-Bonferroni correction was applied. There was a significant main effect of inulin on mean reaction time for hits ($F(1,48)=5.15$, $p<0.028$), with slower reaction times after inulin compared to the placebo condition. Again, this was no longer significant after a Holm-Bonferroni correction was applied.

3.6 Mood and Performance in the Afternoon

There were fewer significant effects of inulin in the afternoon and none remained significant after a Holm-Bonferroni correction was applied.

3.7 Gender and Age

Inclusion of gender and age in the analyses did not change the pattern of results.

4. Discussion

The study reported here examined the acute effects of a large dose of inulin. The results showed that the number

of motions occurring after inulin increased, as did the number of stools passed. As for mood and the performance tasks, the overall effect of inulin appeared to be negative, although this was largely restricted to the morning. Ingestion of inulin was associated with both reduced alertness and a reduction in hedonic tone. Accuracy of recall was poorer on episodic memory tasks and speed of semantic processing was slower. The fact that these effects occurred very rapidly after ingestion suggests that they were not due to changes in gut flora in the colon. This study of acute digestive symptoms confirms that behaviour is impaired by minor illness. Other research on minor illness and behaviour has examined upper respiratory tract illnesses (see Smith, 2013 for a review) and acute symptoms such as headaches (Smith, 2016). Beneficial acute effects of inulin were observed in an earlier study (Smith et al., 2015) when the dose was lower and when it was combined with carbohydrate (similar to the afternoon dose given in the present study).

The research described in this article aimed to provide additional information on the brain-gut axis which refers to the bi-directional signalling between the gastrointestinal tract and the brain. The research did not aim to identify underlying mechanisms but was intended to investigate behavioural changes that could be examined in future research with additional outcomes that would provide a better understanding of what underlies the effects of inulin. It is important, however, to show that plausible mechanisms exist. There have been a number of reviews describing how the microbiome influences the brain (e.g. Cryan and Dinan, 2012; Gaman and Kuo, 2008; Grenham et al., 2011). Three main pathways have been distinguished: endocrine, immune and neural. The microbiota can influence the brain through the hypothalamic-pituitary axis (Sudo et al., 2004), the vagus nerve (Oriarch et al., 2016), tryptophan metabolism (Kennedy et al., 2016), immune activation (Emy et al., 2015), changes in neurotransmitters such as noradrenaline and dopamine (Dinan et al., 2013), the production of short-chain fatty acids which have some neuro-active properties (Sampson and Mazmanian, 2015) and the regulation of central neurotransmitter levels and receptor expression by bacteria (Kennedy et al., 2016).

The brain-gut axis is regulated by a number of mechanisms and some are going to be important for acute effects and others, such as those due to changes in bacteria in the colon, are going to involve mechanisms that take a longer time to be activated (Desmedt et al., 2019). The first definition of a prebiotic (Gibson and Roberfroid, 1995) focused on the stimulation of bacteria in the colon to improve health. More recently a broader definition has been put forward (Gibson et al., 2017), with a prebiotic being defined as "a substrate that is selectively utilized by host microorganisms conferring a health benefit". The presence of multiple underlying mechanisms means that even similar methodologies can lead to different effects if the dose of oligofructose-enriched inulin is varied, the length of the study manipulated, and the oligofructose-enriched inulin ingested with or without carbohydrate. This view can plausibly account for the variation seen in the behavioural effects of inulin in the three studies we have carried out.

The first set of mechanisms that need to be considered are those which might account for short term effects of oligofructose-enriched inulin. A recent review of human studies of prebiotics (Desmedt et al., 2019) discusses the possibility that prebiotics influence the brain independently of changes in gut flora (Savignac et al., 2013). Prebiotics like oligofructose-enriched inulin could directly interact with the gut mucosa and lead to an immune response that influences the brain (Savignac et al., 2013). Prebiotics are not digested by enzymes but are fermented by bacteria in the proximal colon. As a consequence of this fermentation gases, lactate and short-chain fatty acids such as butyrate, acetate and propionate will be released (Slavin, 2013). Animal studies show that prebiotics can modulate various neurotransmitters, and neural growth factors such as brain-derived neurotrophic factor and N-methyl-D-aspartate receptor units (Savignac et al., 2013; Williams et al., 2016). This could provide a mechanism for prebiotics to influence mood and cognition. In addition, studies of both animals (Savignac et al., 2013) and humans (Cani et al., 2009) show that prebiotics can directly influence hormones such as peptide YY and glucagon-like-peptide-1. Desmedt et al. (2019) also acknowledge that discomfort due to flatulence could change affect and cognition which might counteract other beneficial mechanisms. This would appear to be a plausible mechanism underlying effects observed here. Indeed, the negative effects of such digestive problems reported here, appeared to be far greater and widespread than the benefits that could reflect changes in the bacteria in the colon. In acute interventions, oligofructose-enriched inulin could influence levels of blood glucose which might underlie effects on memory (Smith et al., 2015). The oligofructose-enriched inulin could also influence glucose intolerance and insulin resistance which are also known to alter cognition (Watson and Craft 2006).

One must now examine the mechanisms that could underlie behavioural effects of inulin that plausibly reflect changes in bacteria in the colon. These were initially considered by Smith (2005) and can be summarised as follows. The first mechanism involves the production of short-chain fatty acids which have been shown to have neuro-active properties (Sampson and Mazmanian, 2015). Fibre is fermented to short chain fatty acids by gut

flora. Acetate goes to muscle and ATP is generated. As described above, short-term fatty acids also have neuro-active properties. Gut fermentation and subsequent use of short-term fatty acids can contribute significantly to a person's energy requirements. The second possible mechanism is detoxification. Clostridia are known to form neurotoxins and these come from protein metabolism not from carbohydrate or fibre. Fibre stimulates benign flora (bifidobacteria, lactobacilli) that cannot make toxins. These two effects of prebiotics may occur at different speeds, with detoxification being relatively slow.

The present study has a number of limitations, the most obvious being the lack of appropriate measures to identify underlying mechanisms. In order to examine the gut-brain axis it will be important to adopt innovative and methodologically sound approaches. These could involve metagenomics, metatranscriptonomic and metaproteonomic analysis (Desmedt et al., 2019). Highly sensitive gas or liquid chromatography combined with mass spectroscopy will allow measurement of changes of key metabolites in biological fluids. Imaging mass spectroscopy will allow a clearer profile of the dialogue between gut microbes and the brain. The study of pre-biotic effects has involved faecal sampling but it will now be important to also use other invasive techniques to examine microbiota activity in the upper part of the gut (Desmedt et al., 2019).

In conclusion, the results from the present study add to our knowledge of gut-brain interactions. They suggest that there is a need to consider multiple mechanisms which means that a great deal of additional measurement of physiological changes is required to identify the causes of specific effects. The need for the appropriate measurement of the microbiota is essential to establish any claims for prebiotic effects. The presence of a range of underlying mechanisms suggests that it is important to consider appropriate indicators of them in order to understand what underlies specific behavioural changes.

Conflict of interest

The author declares no conflict of interest.

Funding

The study described in this paper was funded by Orafti.

Acknowledgements

I would like to thank Gary Christopher and David Sutherland for assistance with data collection.

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