Impact of sugar replacers on cognitive performance and function in rats

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Glycaemic responses to the dextrin NUTRIOSE®6 (Dex) and the MALTISORB® maltitol (Mal) have been studied previously but their effects on vigilance and cognitive performances are still not known. The present study assesses dose-related glycaemic responses following Dex administration and the hypothesis that Dex and Mal could modulate the glycaemic response, improve vigilance under stress conditions and improve cognitive performances in rats. The glycaemic responses following Dex and corn syrup GLUCIDEX®IT 21 (CoS) solutions at 0.3, 0.5 and 1.0 g/kg body weight administered by oral administration (experiment 1) and glycaemic responses to three cereal bars (standard (CoS), Dex or Dex/Mal bar) (experiment 2) were evaluated. Rats having eaten cereal bars were submitted to vigilance and aversive light stimulus avoidance conditioning tests to assess their vigilance and cognitive performances. The first experiment showed that the glycaemic response to both products is dose-related and that CoS induced a glycaemic response three times higher than the Dex response. The second experiment showed the same glycaemic response for the three cereal bar-treated rats. Yet, an increase in the vigilance of Dex/Mal-treated rats as well as a better discrimination between two levers in the cognitive test for Dex- and Dex/Mal-treated rats were noticed. These results suggest that the glycaemic response is not the only factor to be considered in predicting the efficiency of a food ingredient on vigilance and cognitive performances: these behaviours are improved after Dex- and Mal-prepared cereal bar ingestion whereas the glycaemic response does not differ from the CoS-prepared bar.

NUTRIOSE®6 (Dex) is a food dextrin composed of α-1,4 and α-1,6 linkages and non-digestible glucoside linkages(31). These structural properties explain why this soluble fibre is incompletely hydrolysed and absorbed in the small intestine. About 15 % is absorbed in the small intestine and about 75 % is fermented in the large intestine. The fermentation process occurs along the whole digestive tract and there is no excessive fermentation in the large intestine. The remainder (about 10 %) is excreted in the faeces. Because Dex is fermentable and losing, it is possible in the colon through SCFA production. Moreover, Dex exhibits a very low glycaemic index (GI) of 25 and a low insulinemia index of 13(21). Dex is mainly used for fibre enrichment in plenty of foodstuffs. MALTISORB® maltitol (Mal) is a cereal-derived sugar substitute of the polyl family. The metabolic fate of Mal is about 30–40 % digestion in the small intestine and about 60–70 % fermentation in the colon(31). Its energy value is considered to be 10.0 kJ/g (2.4 kcal/g) and its sweetness is 0.8 £ sucrose (by weight). This sugar alcohol is classified in the very low GI category. The glycaemic response has been estimated to be 29 and the insulinaemic response to be 33 in healthy subjects(33). Mal is mainly used in the production of sugar-free confectionery, chewing gum and chocolate.

Dex and Mal are interesting ingredients for the food industry to manufacture foods that do not induce a high postprandial increase in blood glucose. As they are sugar-free food ingredients, they can be used in replacement of sugar in sugar-free or reduced-in-sugar foodstuffs.

The addition of fibres as well as polyols or the substitution of sugar by fibres or polyols in the diet slows down the absorption of glucose(4) and decreases the glycaemic response(3,5,6). Because they combine slow glucose release in the small intestine with slow energy release in the colon through SCFA production, Mal and Dex deliver energy more progressively than starch or sugars, which are totally hydrolysed in the small intestine. Indeed, foods with a high GI produce a higher postprandial glycaemic peak and a greater overall blood glucose kinetic after consumption than do foods with a low GI(7).

Moreover, the effect of the carbohydrates ingested could play an important part in the physiological and metabolic response. As glucose is the main metabolic fuel of the cells, the modulation of the amplitude of the postprandial hyperglycaemia could be of great importance in terms of physical and cognitive performances of individuals(34). Concerning vigilance...
performances, foods with specific glucose kinetics have to be recommended according to the type of exercise: foods with low glycaemic response before physical exercise and foods with high glycaemic response near the exercise to improve vigilance performances during the physical effort. As cognitive performances depend on the increased inflow of glucose into the brain cells, capacities for attention, memory and learning discrimination are optimised after the addition of low-GI foods to the diet.

The objectives of the present study are to test the hypothesis that Dex and Mal could modulate the glycaemic response, improve vigilance under stress conditions and improve the cognitive performances in rats. The aim of the first experiment is to establish a dose-related glycaemic response following Dex administration. As carbohydrates in different food matrices can produce widely different blood glucose responses, the second experiment assesses the glycaemic response following consumption of cereal bars formulated with Dex, mixed or not with Mal. In this second experiment, the effect of Dex and Mal consumption on vigilance and cognitive performances are measured.

Materials and methods

Animals

Male Wistar/AF EOPS rats (Charles River Laboratories, Saint-Germain sur l’Arbresle, France) were acclimatised for 1 week before the start of testing. At the start of experiments, rats weighing 310 ± 10 g were divided into nine groups. They were housed in a well-controlled environment (20 ± 1 °C; humidity 50 ± 5 %) with a reversed light cycle (lights from 21.00 to 09.00 hours). Feed (M 20; Dietex, Saint Gratien, France) and tap water were provided ad libitum. Rats used in the present study were treated according to rules published by the Association for the Study of Animal Behaviour Ethical Committee (11) and the Canadian Council on Animal Care (12,13). All standard operating procedures were in compliance with the European Community Council Directive 86/609/EEC of 24 November 1986 (14) on the approximation of laws, regulations, and administrative provisions of the Member States regarding the protection of animals used for scientific purposes.

Products

In experiment 1, GLUCIDEX® FT 21, a corn syrup (CoS), and Dex were provided by ROQUETTE Frères (Lestrem, France). CoS was selected as the control, because it is wheat based, as is Dex. CoS is a spray-dried corn syrup obtained after hydrolysis of starch and purification. The dextrose equivalent is about 20–23, its mean degree of polymerisation is 5, and it contains 85.5 % oligo- and polysaccharides, 6.65 % maltose, 2.85 % free glucose and 5 % water. CoS is considered as a totally digestible starch derivative with 16.7 kJ/g (4.0 kcal/g) energy content and a GI near 100 (internal data).

Dex is a purified dextrin processed from starch heated at high temperature and adjusted to a low moisture level in the presence of an acid catalyst. The dextrin obtained is purified with activated carbon and demineralised by ion-exchange resins. Afterwards, the product is chromatographed and the high-molecular-weight fraction is spray-dried to process Dex. The weight average molecular weight and the number average molecular weight are nearly 5000 and 2800 g/mol, respectively, and its mean degree of polymerisation is 17. It contains 85 % total dietary fibre with 76 % of 1,6 linkages and 24 % of 1,2 linkages, 2.3 % reducing sugars and 3.5 % water. The residual content of sugars is below 0.5 % on a dry-weight basis, and thus the dextrin can be considered as sugar free. During the heating step, hydrolysis and repolymerisation occur. Repolymerisation creates new glycosidic bonds such as (1,6), (1,2) and (1,3) linkages in addition to the typical starch α(1,4) and α(1,6) linkages. This point confers to Dex a resistance against the action of endogenous glucidolytic enzymes and permits classification of the product among the soluble dietary fibres with a total fibre content of nearly 85 %.

In experiment 2, three tested cereal bars supplied by ROQUETTE Frères and produced by AAD (Artenay, France) according to an industrial process differed in CoS (standard bar), Dex and/or Mal (ROQUETTE Frères, France) contents. The three cereal bars consisted of cereal mix (39 %), fruits (8 %), sucrose (3 %), sorbitol (3 %), fat (5 %) and chocolate (12 %) as well as CoS (28 % in the standard bar, 19 % in the Dex bar and 12 % in the Dex/Mal bar). The Dex and Dex/Mal bars contained 9 % of Dex and the Dex/Mal bar 7 % of Mal. Their nutritional composition and energy value are given in Table 1. Mal is presented as an anhydrous crystalline white powder containing 99.7 % α-maltitol, 0.1 % water and less than 0.1 % reducing sugars. It is a hydrogenated disaccharide, consisting of glucose and sorbitol, obtained by the hydrogenation of α-maltose. Its molecular weight, very close to that of sugar, is 344 g/mol.

Experiment 1

In order to determine the dose-related glycaemic responses following Dex administration compared with CoS, seventy-two rats were randomly assigned into six groups of twelve rats. Dex or CoS were delivered by intra-gastric administration in 12-h fasted rats at the doses of 0.3, 0.5 and 1.0 g/kg body weight (BW). The glycaemic responses were assessed for 240 min and the glycaemic area under the curve (AUC) was calculated.

Blood glucose was determined using the reflectance photometry method (Glucotrend2; Roche Diagnostics, Maylan, France) according to the following design plan: two basal points at 30 and 5 min before administration of products (by oral administration in experiment 1 and by individual feeding in experiment 2), then every 15 min during the first 1 h after administration of products (at points 15, 30, 45 and 60 min)

Table 1. Composition of the three cereal bars

<table>
<thead>
<tr>
<th></th>
<th>Standard bar (%) DS</th>
<th>Dex bar (%) DS</th>
<th>Dex/Mal bar (%) DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>5-12</td>
<td>5-15</td>
<td>5-21</td>
</tr>
<tr>
<td>Fat</td>
<td>11-15</td>
<td>11-17</td>
<td>11-20</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>68-15</td>
<td>69-49</td>
<td>70-41</td>
</tr>
<tr>
<td>Including sugars</td>
<td>34-76</td>
<td>29-64</td>
<td>25-02</td>
</tr>
<tr>
<td>Fibre</td>
<td>4-33</td>
<td>11-85</td>
<td>12-04</td>
</tr>
<tr>
<td>Energy value (kJ)</td>
<td>1387-31</td>
<td>1348-14</td>
<td>1313-01</td>
</tr>
</tbody>
</table>

DS, dry sample.
and every 30 min during the last 3 h (at points 90, 120, 150, 180, 210 and 240 min).

One drop of blood was sampled on the extremity of the tail and the glucose analysis was immediately carried out. The Glucotrend2 was calibrated with a chip of calibration inserted in the apparatus before use and two control solutions of glucose (Accu-Chek Active Control; Roche Diagnostics) were tested.

Experiment 2

In order to determine the glycaemic response following consumption of 2 g rat of the three cereal bars formulated with different sweeteners as CoS (standard bar), Dex (Dex bar), Dex and Mal (Dex/Mal bars), forty-eight rats were randomly assigned into the three treatment groups, each with sixteen rats.

To avoid any effects due to neophobia during the testing day, small pieces of the tested cereal bars were given in the troughs of the home cages for 3 d to habituate the rats to eat their respective test products. During the next 4 d of the training period, the experimental bars were individually delivered on odd days (days 1, 3 and 5) from 09.00 to 09.15 hours, whereas standard laboratory chow was given on even days (days 2 and 4) at the same hour. This first meal was followed by 4 h starvation until ad libitum feeding was allowed again for the remaining part of the dark phase. This forced fast corresponded to the period necessary to measure the glycaemia during testing on day 5. Rats that did not eat their entire portion were removed from the study.

In experiment 2, glycaemic kinetic measurements were performed as previously described in experiment 1. The AUC of glycaemia obtained with the three cereal bars were calculated taking into account the mean between the two basal points.

To assess the cognitive performances of rats, a wash-out period was observed followed by two more experimental days (days 12 and 13). Rats received 2 g of cereal bars in the same conditions as described in the glycaemic kinetic test.

On day 12, 150 min after administration of the cereal bars, the rats were individually placed in a stressful swimming situation, 20 min before placing them in the aversive light stimulus to test their cognitive ability to escape from this aversive situation and how much the improvement of their cognitive performance was resistant to an increased energy demand. For that, the rats were submitted to a physical workload in the apparatus before use and two control solutions of glucose (Accu-Chek Active Control; Roche Diagnostics) were tested.

The preliminary forced swim step was done to physically exhaust the rats. Immediately after the exercise, rats were dried with a towel and then returned for 20 min to their home cages before the cognitive testing.

The aversive light stimulus avoidance conditioning test was performed by placing the animals in a strongly illuminated (1200 lux) cage (50 × 40 × 37 cm) equipped with two levers. By pressing the active lever the rats switched off the light for 30 s, whereas the inactive lever had no effect on the environment. The test lasted 20 min. The total number of pressings on the two levers was recorded and the learning performance (for example, discrimination between the two levers) was determined by comparison of the numbers of active lever and inactive lever pressings recorded during the light period.

Statistics

An ANOVA or Kruskal–Wallis test was used to compare the various studied variables in the groups. When significant, a post hoc unpaired t test (two-tailed) or Mann–Whitney test was performed. The results are expressed as mean values with their standard errors. For all the comparisons, differences were considered significant at P < 0.05. All statistical analyses were carried out using the StatView® statistical package (SAS Institute, Inc., Cary, NC, USA).

Results

Experiment 1

For the two tested products administered at three different dosages, the maximum of glycaemia was obtained 15 min after their administration (Fig. 1). A dose-related response was observed for each product and CoS provokes the highest response at the three doses compared with the glycaemic response of Dex-treated rats. The weakest response was observed with Dex at 0.3 g/kg BW.

The ANOVA showed a significant difference between the glycaemic kinetics obtained 15, 30, 45 and 60 min after administration of the tested products (Fig. 1). The comparison of CoS with Dex showed significant differences all along the 15 (t = 7.73; P < 0.001), 30 (t = 3.88; P < 0.001), 45 (t = 3.94; P < 0.001) and 60 (t = 3.68; P < 0.005) min at the same dose of 1.0 g/kg BW. Significant differences appear at 15 min between the two products at the doses of 0.3 (t = 3.82;
Experiment 2

For the three cereal bars tested, two peaks of glycaemia were observed: the highest peak was obtained 15 min after the administration of the bars and a second one appeared at 45 min for Dex and Dex/Mal bars and at 60 min for the standard bar after their administration. Twelve rats of the standard group, fifteen rats of the Dex group and thirteen rats of the Dex/Mal group had eaten their entire portion of cereal bars and were included in the statistical analysis. The ANOVA did not show significant differences between the glycaemic kinetics of the three cereal bars and between the AUC of the glycaemic kinetics of the three bars (Fig. 3).

In the stressful swimming situation, the Kruskal–Wallis test showed a significant difference between the latency to seize the rod of the three groups of rats (Table 2). As shown in Table 2, the rats of the Dex/Mal-bar group gripped the rod and climbed on to the top faster than those of the standard- and Dex-bar groups (latency to grip the rod: \( U = 110 \) \( P < 0.001 \); \( U = 35.5 \) \( P < 0.005 \), respectively, and latency to climb up to the top of the rod: \( U = 16.5 \) \( P < 0.05 \); \( U = 40.5 \) \( P < 0.005 \), respectively).

Regarding cognitive performance (Table 3), there is a trend towards significance between the total number of pressings (active lever + inactive lever) for the 20 min testing period between the rats of the three groups.

The Wilcoxon t test showed that the rats of the Dex/Mal-bar group discriminated significantly the active lever from the inactive lever from the first 5 min to the end of the aversive light stimulus avoidance conditioning test \( P < 0.001 \) at 5, 10, 15 and 20 min; they pressed the active lever twice more than the inactive lever. The rats of the Dex-bar group discriminated significantly the two levers after 15 min of test \( P < 0.005 \) whereas the rats of the standard-bar group did not discriminate the two levers during the whole test (Fig. 4). The rats that did not eat the entire portion or did not press the two levers at least once were discarded from the statistical analysis: nine rats were included in the statistical analyses for the standard bar, fourteen rats for the Dex bar and eleven rats for the Dex/Mal bar.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Latency to grip the rod (s)</th>
<th>Latency to climb up to the top of the rod (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
</tr>
<tr>
<td>Standard bar (n 9)†</td>
<td>63.0</td>
<td>8.9</td>
</tr>
<tr>
<td>Dex bar (n 15)†</td>
<td>48.9</td>
<td>7.2</td>
</tr>
<tr>
<td>Dex/Mal bar (n 11)†</td>
<td>23.3</td>
<td>4.2</td>
</tr>
<tr>
<td>Kruskal–Wallis test</td>
<td>( H(2df) = 10.46 )</td>
<td>( P &lt; 0.01 )</td>
</tr>
</tbody>
</table>

*For details of the cereal bars and procedures, see Table 1 and Materials and methods.
† The rat that did not eat its entire portion was discarded from the statistical analysis.

![Fig. 2. Mean glycaemic area under the curve (AUC) after either corn syrup GLUCIDEX®IT 21; ( ), or dextrin NUTRIOSE®6 (Dex; [ ]) administration. Values are means, with standard errors represented by vertical bars. The AUC of Dex at 0·3 g/kg and the AUC of CoS at 1·0 g/kg are similar (-·-·-). *** Mean value was significantly different from that of the Dex-fed group \( (P < 0.001) \) (ANOVA).](https://www.cambridge.org/core/core/terms, https://doi.org/10.1017/S0007114508971294)
Dex and Mal are known for their sugar-replacement properties. They are low-digestible carbohydrates inducing very low glycaemic and insulinemic responses and very little energy. In the present study, a dose-related response is observed between the postprandial glycaemia and the amount of CoS and Dex administered to rats. At each dose, the glycaemic kinetics and AUC of Dex are lower than the corresponding dose of CoS. At the dose of 1 g/kg BW, the glycaemic kinetic of Dex is three times lower than the kinetic of CoS. The AUC of CoS is about twice lower than the AUC of Dex. The shape of the curve with 1 g CoS/kg BW, that is to say a standard maltodextrin, is in agreement with a glucose response obtained in similar conditions (L Deremaux and D Wils, unpublished results). The maltodextrin might be digested and absorbed as quickly as glucose alone, confirming the observation of Macdonald & William. CoS can be replaced by Dex to reduce the postprandial glycaemic kinetics of rats. By extrapolation of these results, Dex could be useful to substitute sugars in beverages, which are simple food matrices.

For the three individual feedings, 56 to 81 % of the rats of the standard group, 69 to 94 % of the rats of the Dex/Mal group and 94 to 100 % of the rats of the Dex group eat the entirety of the portions of cereal bars. This indicated that the presence of dextrin and polyol in the cereal bars did not alter the taste of these bars and seemed to improve it comparing with the interest of rats for the standard bar.

Moreover, these conclusions can be linked with ingestion of the Dex and Dex/Mal cereal bars, because their glycaemia increased rapidly but did not reach the maximum value obtained with administration of pure standard maltodextrin in the first experiment (1.37 g/l for cereal bar v. 1.70 g/l for pure product) and it decreased slowly, indicating that the insulinemic response would have been weak.

In humans, Mal is known to cause a lower rise in blood glucose and insulin levels (GI = 29 and insulinemic index = 33) than a corresponding dose of glucose. It has been demonstrated that Dex involved a glycaemic response of 2.5 and an insulinemic response of 13 in normal subjects.

The weak glycaemic response of both Dex and Mal cannot explain the results observed for the cereal bars because the starch content plays a major role in the glycaemic response, as explained above. As the opposite of starch, low-digestible carbohydrates induce colonic fermentations providing energetic substrates, the SCFA, over a longer period of time.

Under some severe stress conditions and increased energy demand, it has been observed that vigilance, reaction time, attention and reasoning are impaired. In our stressful swimming situation, the results showed that rats of the Dex/Mal-bar group displayed better performances by gripping the rod and climbing up to the top faster than those of the standard- and Dex-bar groups. This could be explained by the better glycaemic status of rats fed with the Dex/Mal bar, allowing a high stress resistance and/or better visual information processing under the stressful conditions in water. Indeed, it has been shown that acute hypoglycaemia impairs visual information processing in healthy human subjects.

Rats receiving Dex or Dex/Mal showed the best cognitive performances than those treated with CoS, 3 h after the administration of the cereal bars and after a physical exercise of 5 min. This physical exercise increased carbohydrate utilisation and permitted amplification of the difference in learning performances between the three groups of rats. Despite a trend towards significance, the total number of lever pressings was not statistically different with groups of sixteen rats, but rats fed with sugar replacers seemed to be more active than the controls and the discrimination between the two levers was improved with Dex/Mal and with the Dex bars.

It has been demonstrated that a typical breakfast of cereal rich in complex carbohydrates can help maintain mental performance (attention and memory) over the morning. Similarly, it has been shown that children’s performance declines throughout the morning and that this decline can be significantly reduced following the intake of a low-GI cereal as compared with a high-GI cereal on measures of accuracy of attention and memory.

Other experiments need to be carried out to explain why the animals that were fed low-digestible carbohydrates improved their vigilance and learning performance in stressful conditions. One hypothesis could be that low-digestible carbohydrates induce a better management of the energy resources as postulated by Benton et al. (8), the H2 excretion indicates the fermentation by gastrointestinal bacteria of Dex and Mal and when these fermentations occur. Van den Heuvel et al. observed that for Dex, the beginning of fermentation occurs 5 h after ingestion. For maltitol, Storey et al. have demonstrated that the delay was of 2.5 h. One can assume that production of SCFA begins at...
the same time and lasts a few hours after the start of the fermentation. Digestion in the small intestine associated with colonic fermentation explains the prolonged energy supply of certain foodstuffs or food ingredients such as soluble dietary fibres and sugar alcohols.

**Conclusion**

The glycaemic kinetics of a finished product is not sufficient to predict its effect on vigilance and cognitive performances. The incorporation of Dex and Mal in the bars influences the learning performances of the rats, whereas the glycaemic kinetics is similar for the three groups.

Dex and/or Mal, in combination or alone, can induce a better control of the energy resources that can be very helpful in children’s nutrition and more generally in healthy nutrition.

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