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Inulin/oligofructose and anticancer therapy

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The results of our investigations indicate that dietary treatment with inulin or oligofructose incorporated in the basal diet for experimental animals: (i) reduced the incidence of mammary tumors induced in Sprague-Dawley rats by methylnitrosourea; (ii) inhibited the growth of transplantable malignant tumors in mice; and (iii) decreased the incidence of lung metastases of a malignant tumor implanted intramuscularily in mice. Moreover, besides such cancer risk reduction effects, the dietary treatment with inulin or oligofructose significantly potentiated the effects of subtherapeutic doses of six different cytotoxic drugs commonly utilized in human cancer treatment. If confirmed, such dietary treatment with inulin or oligofructose potentiating cancer therapy might become an interesting approach to complement classical protocols of human cancer treatment without any additional risk for the patients.

Inulin/oligofructose: Anticancer therapy

Introduction

The effect of nutrition on tumor incidence and growth is a subject of major interest (Williams & Dickerson, 1990; Roberfroid, 1991; Milner, 1994) and amongst the most frequently investigated dietary components, the non-digestible carbohydrates generally classified as dietary fibers play a major role (Roberfroid, 1993; Cohen *et al.* 1996).

This paper is a review of the effects of two soluble dietary fibers, inulin and oligofructose, in various experimental models used to study the cancer risk reducing capacity of dietary factors.

Anticarcinogenic and tumor growth inhibitory effects

Our initial research has demonstrated that oligofructose incorporated (15 % w/w) in the basal diet for experimental animals reduced the incidence of mammary tumors induced in Sprague-Dawley female rats by methylnitrosourea. The number of tumor bearing rats and the total number of mammary tumors were significantly lower in the oligofructose fed rats than in the rats of the control group fed a basal diet (Taper & Roberfroid, 1999).

Similar treatment with an inulin or oligofructose containing diet also reduced the growth of intramuscularly transplanted solid mouse tumors originating from two different tumor cell lines (transplantable liver tumor, TLT) and mammary mouse carcinoma (EMT6, Taper *et al.* 1997). This tumor growth inhibitory effect has been confirmed in mice fed inulin or oligofructose on an ascitic form of the intraperitoneally transplanted malignant liver tumor (TLT). The percentage of increase in life span (ILS), when compared with the control group of mice fed a basal diet alone, was 16 % and 18 % for inulin and oligofructose supplemented diets respectively (Taper *et al.* 1998).

Antimetastatic effects of oligofructose or inulin

The most surprising activity of inulin or oligofructose is the capacity to significantly reduce the number of mice bearing lung metastases as well as the absolute number of lung metastases per group after intramuscular transplantation of the TLT tumor in young male C3H mice. The percentages of mice bearing lung metastases in a control group fed basal diet, in an inulin fed group and in an oligofructrose fed group were 59, 36 and 35 % respectively. The total number of lung metastases was thirty-seven, eighteen and sixteen respectively, for the three groups (Taper & Roberfroid, 2000).

Potentiation of cancer chemotherapy by dietary inulin and oligofructose

Both inulin and oligofructose have also been shown to potentiate the therapeutic effects of all six investigated cytotoxic drugs that are representatives of the different groups of cytotoxic drugs classically used in human

Abbreviations: ILS, increase in life span; TLT, transplantable liver tumor.

Note: For the definition of the terms inulin and oligofructose please refer to the introductory paper (p. S139) and its footnote.

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cancer treatment. In order to demonstrate such a potentiation of the therapeutic effect, inulin or oligofructose fed mice were intraperitoneally injected with a single and subtherapeutic dose of the drugs and increased in life span (ILS) was calculated. All these experiments were performed using the ascitic form of a transplantable liver tumor (TLT, Taper *et al.* 1966, Cappucino *et al.* 1996) injected intraperitoneally to young adult male mice of the NMRI strain. Mortality rates are expressed as the increase of life span (ILS) which was compared with that of the control, untreated group of mice and calculated according to the NCI recommendations (Geran *et al.* 1972).

As shown in Table 1 the potentiation of the effects of the chemotherapies induced by the adjuvant treatment with inulin and oligofructose, was, in more than 50 % of the experiments, a synergistic effect. The results of the remaining experiments were also positive but they corresponded with an additive effect. A negative result of the adjuvant therapy induced by inulin or oligofructose was never observed. Distinct differences in the chemotherapy potentiating action between inulin and oligofructose did not exist. Quantitatively the adjuvant therapeutic effect was somewhat different for the different drugs. In some experiments a spectacular effect was observed, as for cyclophosphamide a drug for which the therapeutic effect was increased by 47 % (increased ILS) by inulin. A detailed analysis of the mortality diagrams was also performed for each experiment. The mortality curves were in most experiments distinctly prolonged by the adjuvant treatment with inulin or oligofructose and usually on the whole length of curve from the first to the last death. In such mortality curves, the difference between the treated groups (receiving only cytotoxic drugs, or only dietary fructans, or both) and the untreated absolute control group was statistically analyzed using a Log-Rank test. The conclusion of such an analysis is that the therapy potentiating effect of both inulin and oligofructose on cancer chemotherapy is very highly significant ($P<0{\cdot}001$) in eight of a total of twelve experiments. The results of the remaining four experiments are highly significant ($P<0{\cdot}01$). No gastro-intestinal troubles were observed in any of the animals fed, from the start of the experiment, a diet containing 15 % of inulin or oligofructose into the diet.

Inulin or oligofructose fed alone did not influence the body weight growth when compared with the untreated control group fed the basal diet and they did not induce any alteration in histologically examined main organs, as

Table 1. Effects of inulin and oligofructose on the increase in lifespan induced by a single dose of different cytotoxic drugs, administered to ascitic TLT bearing NMRI mice. Each of the treated groups of twelve mice had its individual untreated control to which it was compared when calculating the increase in lifespan (ILS). The results are the means of two experiments performed at different periods except the last three experiments which were performed only once with ten mice/group. The Log-Rank test was applied to test for the difference in the ILS values which was considered significant, highly significant and very highly significant for $P<0{\cdot}05$, $0{\cdot}01$ and $0{\cdot}001$, respectively

Treatment	ILS (%)	Statistical significance	Effect of combined treatment
5-Fluorouracil	18·75		
Oligofructose	12·5		
5-Fluorouracil+Oligofructose	40·6	$P<0{\cdot}001$	Synergistic
5-Fluorouracil	6·25		
Oligofructose	12·5		
Inulin	12·5		
5-Fluorouracil+Oligofructose	21·9	$P<0{\cdot}001$	Synergistic
5-Fluorouracil+Inulin	18·75	$P<0{\cdot}001$	Additive
Doxorubicine	14·7		
Oligofructose	5·9		
Doxorubicine+Oligofructose	17·6	$P<0{\cdot}001$	Additive
Vincristine	33·3		
Oligofructose	13·3		
Inulin	10·0		
Vincristine+Oligofructose	46·7	$P<0{\cdot}001$	Additive
Vincristine+Inulin	43·3	$P<0{\cdot}01$	Additive
Cyclophosphamide	11·0		
Oligofructose	16·0		
Inulin	11·0		
Cyclophosphamide+Oligofructose	44·0	$P<0{\cdot}01$	Synergistic
Cyclophosphamide+Inulin	47·0	$P<0{\cdot}001$	Synergistic
Methotrexate	2·0		
Oligofructose	5·0		
Inulin	11·0		
Methotrexate+Oligofructose	29·0	$P<0{\cdot}001$	Synergistic
Methotrexate+Inulin	20·0	$P<0{\cdot}01$	Synergistic
Cytarabine	3·0		
Oligofructose	15·1		
Inulin	15·1		
Cytarabine+Oligofructose	15·1	$P<0{\cdot}01$	Additive
Cytarabine+Inulin	27·2	$P<0{\cdot}001$	Synergistic

already known from other experiments previously published (Taper *et al.* 1997, 1998; Taper & Roberfroid, 1999). Moreover, inulin and oligofructose did not increase either the general or the organ toxicity induced by the cytotoxic drugs.

Hypothetical mechanisms of anticancer effects of inulin or oligofructose

Several hypothetical mechanisms are probably involved in the cancer growth inhibition and cancer therapy potentiating effects of inulin or oligofructose. These carbohydrates are non-digestible by endogenous enzymes, but they are actively fermented by the colonic bacteria, selectively promoting the growth of some of them, especially the bifidobacteria (Gibson *et al.* 1995; Wang & Gibson, 1993). Such changes in the composition of the colonic microflora have been reported to reduce tumor incidence and/or growth (Reddy *et al.* 1973; Reddy & Rivenson, 1993). Moreover, it has been reported that cell wall preparations from *Bifidobacterium infantis* have a tumor suppressive effect (Tsuyuki *et al.* 1991; Sekine *et al.* 1994) and it has also been shown that inulin and oligofructose reduce the incidence of aberrant crypt foci in the colon of rats previously injected with a chemical carcinogen (Reddy *et al.* 1997; Rowland *et al.* 1998).

The growth and proliferation of tumor cells is known to be dependent on glucose availability, because these cells acquire the major part of their energy from the glycolytic pathway (Cay *et al.* 1992). The non-digestible carbohydrates have been reported to decrease the serum glucose level in rats and humans (Yamashita *et al.* 1994; Kok *et al.* 1996) an effect that might deprive cancer cells of their essential substrate.

Kuhajda *et al.* (1994) have demonstrated that, *in vitro*, human cancer cells do require endogenous fatty acid synthesis for their growth, and that the inhibition of this metabolic pathway can be considered as a new and promising target for cancer therapy. Recent experiments have demonstrated that inulin and oligofructose, which inhibits tumor growth, also decrease triglycerides, phospholipids and very low density lipoproteins in serum by lowering the *de novo* lipogenesis in the liver (Kok *et al.* 1996; Fiordaliso *et al.* 1995). Such a metabolic effect might also be related to the tumor inhibitory effect reported above.

Conclusions

More advanced investigations are necessary to elucidate further which of the above mentioned or other mechanisms are essential for the cancer risk reducing and cancer chemotherapy-potentiating effects of dietary inulin and oligofructose. Such non-toxic dietary components might however prove to be very useful. Moreover, further investigations are presently being undertaken to find out whether the effects of another, classical cancer treatment, e.g. radiotherapy can also be potentiated. Inulin or oligofructose and preliminary results seem indeed to confirm such an effect (in preparation for publication).

Further investigations on these topics may lead to an improvement of the efficacy of cancer chemotherapy by allowing a potentiation of classical clinical treatments. If further proven, such an effect will support the proposal to test and hopefully introduce, into classical protocols of human cancer treatment, a new, non-toxic and easily applicable adjuvant therapy with no additional discomfort for the patients.

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