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Recent developments in modifying crops and agronomic practice to improve human health ☆

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ABSTRACT

Malnutrition of micronutrients (vitamins and minerals) affects more than two billion people worldwide, especially in developing countries, largely due to low concentrations or poor bioavailability of these nutrients in the diet. In contrast, over-consumption, particularly of over-refined cereal-based foods, has contributed to the development of an "epidemic" of metabolic diseases in some developed countries. This review highlights recent progress in modifying crops and agronomic practice to increase health benefits. Mineral concentrations or bioavailability in crop edible parts can be increased by fertilisation, breeding or biotechnology. It is also possible to modify crops using transgenic technology to enable or increase the biosynthesis of vitamins and long chain omega-3 polyunsaturated fatty acids, or to modify the composition of starch or dietary fibre. Although technologically feasible now or in the near future, the development of micronutrient biofortified or composition-modified crops would also depend on other factors such as consumer acceptance, cost, regulations and national or international intervention.

Introduction

Currently over one billion people worldwide are undernourished due to insufficient food (FAO, 2009). Yet, more than two billion people suffer from "hidden hunger", a term used to describe malnutrition of micronutrients (vitamins and minerals that are required at small quantities) (Kennedy et al., 2003). Humans require at least 20 mineral elements, 13 vitamins, 9 amino acids and 2 fatty acids (Graham et al., 2007; Welch and Graham, 2004). Deficiency of iodine (I), iron (Fe) and zinc (Zn) each affects about 35%, 40% and 33%, respectively, of the world population, and of vitamin A more than 40% of children (The World Bank, 2006). Micronutrient malnutrition is most prevalent in developing countries, with deficiencies of Fe, Zn and vitamin A being among the ten leading causes of illness and disease in low-income countries (WHO, 2002). Other nutrients, such as calcium (Ca), magnesium (Mg), copper (Cu) and selenium (Se), may also be inadequate in the diets of some people (Stein, 2010; White and Broadley, 2009). The number of people having insufficient Se intake is estimated to be between 0.5 and 1 billion people worldwide (Combs, 2001). Widespread micronutrient malnutrition has enormous socio–economic consequences, resulting in increased mortality and morbidity, impaired growth, development and learning ability in infants and children, and loss in work capacity of adults; these in turn undermine economic growth and perpetuate poverty (The World Bank, 2006; WHO, 2002). Tackling micronutrient malnutrition is considered to be among the best investments that will generate a high return in socio-economic benefits. (The Copenhagen Consensus 2004; http://www.copenhagenconsensus.com/.) Although less prevalent, micronutrient deficiencies also occur in developed countries. For example, in the UK, the 2000/01 National Diet and Nutrition Survey reported that mean daily intakes of Fe from food sources were less than the lower recommended nutrient intake in 25% of adult women, and of Zn in 4% of all adults (Henderson et al., 2003). The average Se intake of the UK population was below the recommended level (Rayman, 2002).

Agriculture provides the primary source of the nutrients required by humans and farmed animals. Two-thirds of the world's population depend on cereal or tuber-based diets, which tend to satisfy the demand on calories but not essential micronutrients (FAO and WHO, 2001). Tremendous progress has been made over the last 50 years to increase grain production, brought about by the Green Revolution which unleashed the yield potentials of major cereal crops through breeding, fertilisation and crop protection. This is an enormous achievement in terms of feeding a rapidly growing global population. However, modern agriculture has been driven mainly by producing higher yields at lower cost, with hitherto little emphasis on the nutritional quality (Sands et al., 2009). While the nutritional profile of cereals and tubers is not optimal for human or animal nutrition, their success in production has also led to displacement in some countries of legumes and pulse crops, which are nutritionally superior to cereals (Welch and Graham,

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☆ While the Government Office for Science commissioned this review, the views are those of the author(s), are independent of Government, and do not constitute Government policy.

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2004). There is also evidence that some modern varieties of cereals and vegetables contain lower levels of essential minerals than the old ones, either as a result of the dilution brought about by a larger yield or by a shift in the physiology of mineral uptake and distribution (Fan et al., 2008; Garvin et al., 2006; White and Broadley, 2005; Zhao et al., 2009). These factors may have contributed to the increasing proportion of populations with micronutrient deficiency in some countries (Graham et al., 2007; Welch and Graham, 2002). It has been advocated that a new paradigm for agriculture linking farming to human health closely is needed (Graham et al., 2007; Welch and Graham, 2002).

There is a general consensus among human nutritionists that the best way to tackle micronutrient deficiency is through diversification in diet to include pulse, vegetables, fruits, meat and fish (FAO and WHO, 2001). However, this is not always possible, especially for people with a low income. Other strategies include fortification and supplementation; examples include iodine fortification in salt and fortification of bread with vitamin A or folic acid. But these strategies require national infrastructure, purchasing power, or access to markets or health-care systems, which are often inadequate in developing countries (Mayer et al., 2008). Biofortification is an approach aiming to increase micronutrient concentrations in the edible parts of plants through crop breeding or the use of biotechnology; here we use a broader definition to include biofortification through agronomic practices as well (Cakmak, 2008). Biofortification is considered to be potentially more cost-effective than other ways to deliver the benefits of micronutrient enhancement to the rural populations in developing countries (Mayer et al., 2008; Nestel et al., 2006). Research in this area has received strong support from the international consortium HarvestPlus Challenge Programme (http://www.harvestplus.org/) and the Grand Challenges in Global Health Programme (http://www.grandchallenges.org/) funded by the Bill & Melinda Gates Foundation.

Modern methods of food processing also contribute to nutrient deficiencies, by over-refining to remove tissues which are rich in fibre, minerals and vitamins. This is a particular problem with cereals, where milling (of wheat), polishing (rice), pearling (barley) and decortication (sorghum) all remove the health benefits associated with the outer layers of the grain. In the case of wheat the most obvious way to counter this is to increase the consumption of wholegrain products, but these are usually more expensive than those made from white flour and not acceptable by some sectors of the population.

Finally, the development of genetically modified (GM) crops also allows the replacement of animal sources of nutrients by plant foods; this is exemplified below by the discussion of omega-3 long chain polyunsaturated fatty acids (LC-PUFAs).

Here we review recent progress in improving the nutritional quality and health benefits of agricultural produce through agronomy, crop breeding and biotechnology.

Essential mineral nutrients and toxic elements

There are three strategies to increase the density of essential minerals in the edible parts of plants: conventional breeding, biotechnology or agronomy; their applicability depends on mineral elements, soil conditions, crop species and farming system. Some toxic mineral elements may accumulate in food crops to pose a potential health risk.

Breeding for enhanced mineral concentrations

Conventional breeding is the main strategy pursued by the HarvestPlus programme, targeting seven crops (wheat, rice, maize, cassava, pearl millet, bean and sweet potato) that are the staple foods in Asia and Africa. This strategy aims to identify the traits of high mineral (Fe and Zn) concentrations in seeds and introduce them into locally adopted cultivars, with the targets for mineral enhancement set at between 33% and 100% of the baseline concentrations depending on mineral and crop (http://www.harvestplus.org/). A new cultivar of bean with a high Fe concentration in the seeds has already been bred, and it is anticipated that several varieties of micronutrient-rich staple crops should be ready for distribution in the developing world as soon as 2012. The International Rice Research Institute (IRRI) has bred a high Fe rice variety with 4–5-fold higher Fe concentration after processing than conventional varieties (Gregorio, 2002). In a 9-month feeding trial with Filipino women, consumption of the high Fe rice increased total dietary Fe intake by 17%, resulting in a modest increase in serum ferritin and total body Fe (Haas et al., 2005).

There is considerable genotypic variation in the concentrations of Fe and Zn in the seeds or tubers of major crops; for cereals this variation is typically 1.5–4-fold (White and Broadley, 2009). Quantitative trait loci (QTLs) for grain mineral concentrations have been located in a number of crops (e.g. Norton et al., 2010; Stangoulis et al., 2007), which should facilitate molecular marker assisted breeding. Grain Fe and Zn often correlate with each other; thus, it is possible to enhance both minerals simultaneously through genetic improvement. Wild relatives of wheat exhibit a particularly high genetic diversity in seed Fe and Zn concentrations, with some accessions of emmer wheat containing very high concentrations of Zn and Fe (up to 125 mg kg^{-1} and 85 mg kg^{-1}, respectively) as well as a high protein content (Peleg et al., 2008). The introgression of the high grain protein locus (*Gpc-B1*) from wild emmer wheat into a cultivated durum wheat resulted in higher concentrations of Fe, Zn, Mn and protein in the grain (Distelfeld et al., 2007). The gene encoded by the *Gpc-B1* locus and its physiological effects are now known (Uauy et al., 2006; Waters et al., 2009).

Agronomic biofortification through fertilisation and crop diversification

Fertilisation is necessary for those trace elements whose accumulation in the edible parts of plants is limited by the low availability in soil, such as Se, I and, in some soils, Zn. Both Se and I are not essential for higher plants; therefore their low levels in soils are not a limiting factor for plant growth. Soils in much of the western Europe, parts of China and New Zealand are low in Se supply. Finland was the first country in the world to adopt a nation-wide agronomic biofortification strategy by adding a small amount of Se to fertilisers (currently equivalent of 10 g Se per hectare) (Hartikainen, 2005). This practice, begun in 1984, has increased the concentrations of Se in food crops and animal products, and boosted Se intakes in the Finnish population from well below to above the recommended level (Hartikainen, 2005). In the UK, a recent project has demonstrated that wheat grain Se concentration can be increased by approximately 10-fold, to the level commonly obtained in North American wheat, by an addition of 10 g Se/ha to soil (Broadley et al., 2010). The benefits of agronomic biofortification are that organic Se compounds synthesised in plants are more effective than inorganic Se salts and that crops provide a buffer to prevent excessive intake of Se. For I, while fortification in salt is highly effective and used by many countries, it is also possible to biofortify crops which gives benefit to both humans and farmed animals. In Xingjiang province of China, I fertilisation through irrigation water was found to be highly effective in raising I intake and decreasing infant mortality at a low cost (Cao et al., 1994; DeLong et al., 1997). For both Se and I, genetic improvement in crop uptake may have limited effects unless certain amounts of these elements are added to the soil first.

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Approximately half of the world agricultural soils are deficient in Zn for crop production, and these soils are generally associated with Zn-deficient humans (Cakmak, 2008). Zinc concentration in wheat grain typically varies from 20 to 30 mg kg^{-1}, and to have a measurable impact on human nutrition, this needs to be increased by at least 10 mg kg^{-1} (Cakmak, 2008). In Zn-deficient soil, application of Zn fertilisers is effective in boosting both crop yield and Zn concentration in the grain. Trials in Turkey showed that foliar application of $ZnSO_4$ to wheat crop at a late growth stage increased grain Zn concentration by 3-fold, up to 60 mg kg^{-1} (Cakmak, 2008). The dual benefits on crop yield and nutritional quality mean that the fertilisation practice is readily adopted by farmers in Turkey (Cakmak, 2008). Zinc deficiency is also common in lowland rice due to the immobilisation of Zn in the flooded soil (formation of insoluble ZnS and $ZnCO_3$). Native soil Zn status was found to be the dominant factor determining the concentration of Zn in rice grain, followed by rice genotype (Wissuwa et al., 2008). In severely Zn-deficient paddy soils, addition of Zn fertiliser to soil increased yield, but not the concentration of Zn in rice grain, probably due to the effect of Zn immobilisation in soil (Wissuwa et al., 2008). In these soils, foliar applications may be a more effective method to increase grain Zn concentration.

One criticism of the Green Revolution is that it leads to more extensive production of cereals at the expense of legumes and other pulse crops (Welch and Graham, 2002). Diversification of cropping systems to include more nutrient-dense crops would bring considerable benefits to human nutrition in the low-income regions and should be promoted (Graham et al., 2007). The rice-fish system is an excellent example of adding economic and nutrition values to agriculture. There is considerable potential for expansion of this cultivation system, although there are constraints that need to be overcome (Graham et al., 2007). Intercropping between dicots and graminaceous species can lead to a more efficient use of nutrient resources with the additional benefit of achieving higher concentrations of Fe and Zn in seeds (Zuo and Zhang, 2009).

Genetic modification to enhance mineral nutrition for humans

In cases where agronomic and breeding approaches cannot achieve significant improvement in mineral concentration, transgenic techniques offer a useful alternative. Iron and zinc are relevant cases because their concentrations are particularly low in the starchy endosperm which is the part of grain commonly consumed by people, and because their bioavailability to humans is low due to the presence of the anti-nutrient phytate. These hindrances may be overcome by mutagenesis to reduce the synthesis of phytate, by transgenesis to express genes encoding phytase or by expression of genes that lead to accumulation of iron in the endosperm (Brinch-Pedersen et al., 2007). Transgenesis is also important for those crops that are difficult to introduce nutritional traits through conventional breeding, such as banana and cassava. Currently, the Grand Challenges in Global Health Programme supports four biofortification projects that involve transgenic components (http://www.grandchallenges.org/).

Ferritin is a protein nanocage that can store up to 4500 atoms of Fe^{3+} in its interior cavity (Palmer and Guerinot, 2009). Ferritin serves as a primary storage of Fe in animals, but may play a role in preventing oxidative damage caused by excess Fe in plants (Palmer and Guerinot, 2009). Overexpression of the soybean or common bean ferritin gene in rice endosperm resulted in a 2–3-fold increase in the concentration of Fe in rice seeds by increasing the sink for Fe in the endosperm (Goto et al., 1999; Lucca et al., 2001). A larger increase (6-fold) in Fe concentration was achieved in transgenic rice over-expressing both the ferritin gene in the endosperm and the nicotianamine synthase (NAS) gene constitutively in the whole plant (Wirth et al., 2009). Nicotianamine (NA) is a chelator for metals such as Fe and plays an important role in the phloem transport of Fe to grain. Importantly, the increase in Fe was found in the endosperm; so the polishing of brown rice would not diminish the value of enhanced Fe (Goto et al., 1999; Wirth et al., 2009). Furthermore, Fe stored in plant ferritin is as bioavailable to humans as ferrous sulphate (Lönnerdal, 2007). Another approach is to increase the NA level in rice seeds through overexpression of NAS genes, which leads to enhanced bioavailability of Fe (Lee et al., 2009; Zheng et al., 2010).

Phytate accumulates in the aleurone and embryo cells of cereal and legume seeds, and is a potent inhibitor of the absorption of Zn and non-heme Fe from plant sources. Decreasing the phytate content in food can increase the bioavailability of these mineral micronutrients. Mutants of cereals and legumes with much lower levels of phytate content in the grain have been isolated; but these mutants tend to have the undesirable characters of low yielding and poor germination (Brinch-Pedersen et al., 2007). Phytate is degraded by the enzyme phytase during seed germination or food processing (cooking, fermentation). The level of phytase can be enhanced by over-expressing a microbial phytase gene (*PhyA*) (e.g. Drakakaki et al., 2005), or more usefully, a heat-stable phytase so that the enzyme can better withstand high temperatures during cooking or processing (Brinch-Pedersen et al., 2006). Animal feeding studies showed a significant improvement in Zn bioavailability in the transgenic wheat containing a heat-stable phytase (Brinch-Pedersen et al., 2007). Recently, a transgenic maize with enhanced phytase has been approved for commercial production in China; when used in animal feeds, enhanced phytase is expected to help pigs digest more phosphorus and micronutrients, enhancing growth and reducing phosphorus pollution from animal waste (http://www.reuters.com/article/email/idUSSP364484).

Dealing with toxic elements

Toxic elements that are likely to be taken up by crops and accumulated up to levels that may pose a risk to humans include cadmium (Cd) and arsenic (As). In both cases preventing agricultural soils from contamination is the best strategy to avoid their excessive accumulation in the food chain. This is not always possible as a result of the legacy of past industrial pollution, or in the case of south Asia the widespread use of groundwater naturally contaminated with As for irrigation. Crop species and varieties within a species vary widely in the ability to accumulate Cd and As. For example, paddy rice is particularly efficient in As accumulation due to the anaerobic soil conditions and the inadvertent uptake of arsenite through the strong uptake pathway for silicon (Ma et al., 2008). Various methods are being developed to deal with the As contamination problem, including changes in cultivation method and water management (Duxbury and Panaullah, 2007; Li et al., 2009), silicon fertilisation (Li et al., 2009) and variety selection (Norton et al., 2009). Crop breeding can also be used to reduce Cd uptake. Low Cd accumulating cultivars of durum wheat have been successfully bred and released (Clarke et al., 1997). A major QTL and the responsible gene that regulates the accumulation of Cd in shoot and grain of rice have been identified, paving the way for breeding low Cd cultivars of rice (Ueno et al., 2010). Because the uptake of toxic elements by plants is inadvertent through the mechanisms for essential nutrients (an example is the uptake of Cd^{2+} by Fe^{2+} or Zn^{2+} transporters), attempts to boost Zn and Fe uptake need to avoid possible undesirable consequences of increased Cd accumulation (Palmgren et al., 2008). Technologies for remediation of contaminated soils are being developed (Zhao and McGrath, 2009).

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Biofortification of vitamins

Staple foods are deficient in many vitamins because of a lack of the enzymes involved in their biosynthetic pathways. The last decade has seen significant advances in metabolic engineering of these pathways into cereal grain or tubers (for a more comprehensive review, see Hirschi, 2009; Newell-McGloughlin, 2008).

Pro-vitamin A

Vitamin A (retinol) is needed by humans for the normal functioning of the visual system, growth and development, and maintenance of epithelial cellular integrity, immune function, and reproduction (FAO and WHO, 2001). Vitamin A deficiency is prevalent in populations in South and Southeast Asia which rely on rice as the staple food. This is because rice endosperm lacks pro-vitamin A (β-carotene), which is converted to vitamin A in the human body. To overcome this problem, Ye et al. (2000) transformed rice with two key enzymes involved in β-carotene biosynthesis: phytoene synthase (*psy*) originating from daffodil and phytoene desaturase (crtI) from the bacterium *Erwinia uredovora*, with the *psy* gene placed under the control of an endosperm-specific promoter. The best transgenic line produced 1.6 $\mu g\ g^{-1}$ total carotenoids (mainly β-carotene) in the rice endosperm. This transgenic rice is named Golden rice because of its yellow–orange colour due to the presence of carotenoids. The second generation Golden rice (Golden Rice 2) was created by replacing the daffodil *psy* gene with a much more efficient *psy* from maize (Paine et al., 2005). The Golden Rice 2 contains up to 37 $\mu g\ g^{-1}$ total carotenoids (i.e. 23-fold higher than the Golden Rice 1), of which about 80% is β-carotene. Based on a retinol equivalency ratio for β-carotene of 12: 1, 72 g of Golden Rice 2 containing 25 $\mu g\ g^{-1}$ β-carotene would provide half of the recommended dietary allowance for 1- to 3-year-old children (300 μg vitamin A). A recent clinical trial shows that the Golden Rice 2 is an effective source of vitamin A for humans, with a β-carotene to retinol conversion efficiency (3.8:1) much higher than 12:1 (Tang et al., 2009). Both Golden Rice 1 and 2 have been donated to the Golden Rice Humanitarian Board, which is responsible for the global development, introduction and free distribution of Golden Rice to target countries (http://www.goldenrice.org/), and locally adapted varieties of Golden rice are expected to reach the market in 2012 (Potrykus, 2010). In other food crops such as potato, overexpression of a microbial phytoene synthase also significantly enhanced the levels of β-carotene and lutein in the tubers (Ducreux et al., 2005).

In a recent study, Zhu et al. (2008) used a combinational nuclear transformation method to introduce five genes of the carotenoid pathway into a white maize variety, each with a different endosperm-specific promoter. This produced a library of transgenic plants with different combinations of transgenes, including some lines carrying all five transgenes. This study shows that it is now feasible to transform plants efficiently with multiple genes involved in a complex metabolic pathway.

Orange-fleshed sweet potato is excellent source of pro-vitamin A for humans, with some lines containing > 200 $\mu g\ g^{-1}$ β-carotene (Nestel et al., 2006; van Jaarsveld et al., 2005). When this type of sweet potato was introduced into a resource poor area in Mozambique, dietary intake of vitamin A and serum retinol concentrations in the children from intervention households were improved substantially (Low et al., 2007). Current efforts are being made to develop sweet potato varieties that are well accepted by target groups and educating individuals to purchase and consume orange-fleshed varieties (Tanumihardjo et al., 2008). Progress has also been made to biofortify maize with pro-vitamin A carotenoids through breeding (Tanumihardjo et al., 2008).

Folates

Folates (B vitamins) are required for one-carbon transfer reactions and therefore play important roles in nucleotide biosynthesis, amino acid metabolism and the methylation cycle (Bekaert et al., 2008). Humans and animals cannot synthesise folates and need them in the diet. Cereals, particularly rice, are poor sources of folates. Folate intake is suboptimal in most populations in developing countries, as well as some population groups in developed countries (Bekaert et al., 2008). Biofortification of folates in crops is now feasible through metabolic engineering. Folates are tripartite compounds synthesised from pteridine, *p*-aminobenzoate and glutamate precursors. Overexpression of GTP cyclohydrolase I (GTPCHI, a synthetic gene based on mammalian), the first enzyme of pteridine biosynthesis, in tomato fruit increased pteridine content in fruits by 3- to 140-fold and folate content by an average of 2-fold (de la Garza et al., 2004). A much greater increase in folate content (up to 25-fold) was achieved in double transgenic tomato fruit over-expressing both GTPCHI and aminodeoxychorismate synthase (ADCS), the first enzyme of *p*-aminobenzoate biosynthesis (de La Garza et al., 2007). With the level of folate achieved in the transgenic tomato fruit (840 μg per 100 g), less than one standard serving can provide the complete daily requirement for adults (400 μg) and pregnant women (600 μg). The two precursors, pteridines and *p*-aminobenzoate, are also over-produced in the double transgenic plants. While the level of *p*-aminobenzoate is considered harmless for human health, the consequences of increased pteridines are unclear and require more research (Bekaert et al., 2008; de La Garza et al., 2007). A similar approach has been used to produce rice grain with up to 100-fold higher folate content (1723 μg per 100 g) than the untransformed rice (Storozhenko et al., 2007). Furthermore, pteridine content in the transgenic rice was increased by a much smaller extent than that in transgenic tomato, possibly due to the use of a plant (*Arabidopsis thaliana*) GTPCHI in the former which may be subject to negative feedback regulation; this has the benefit of avoiding potential health implications from excess intakes of pteridines. Considering about 45% losses of folates during cooking of rice and assuming 50% bioavailability, consumption of 100 g of the biofortified rice grains can satisfy the daily requirement for adults (Storozhenko et al., 2007).

Vitamin E

Vitamin E is the major lipid-soluble antioxidant in the cell antioxidant defence system, playing an important role in protecting membrane lipids from oxidative damage, and is essential in human and animal diets (FAO and WHO, 2001). Vitamin E comprises of a family of eight naturally occurring tocochromanol compounds, which share a common molecular structure consisting of an aromatic head group and a saturated (tocopherols) or unsaturated (tocotrienols) isoprenoid side chain. Tocopherols and tocotrienols each have four compounds (α-, β-, γ- and δ-), which differ in the number and position of methyl group on the aromatic ring. Among the eight tocochromanol compounds, α-tocopherol has the highest vitamin E activity, followed by β-tocopherol and α-tocotrienol (DellaPenna and Pogson, 2006; FAO and WHO, 2001). All the core enzymes and the coding genes in the biosynthetic pathway of tocochromanols have been isolated and studied, allowing metabolic engineering of these compounds in food crops (DellaPenna and Pogson, 2006). For example, overexpression of the barley homogentisic acid geranylgeranyl transferase (HGGT) in corn seeds increased the total content of tocotrienols and tocopherols by 4- to 6-fold (Cahoon et al., 2003). α-Tocopherol, the most active form of vitamin E, is often the minor component of tocochromanols in plant seeds due to the limitation in two methyltransferases, 2-methyl-6-phytylbenzoquinol methyltransferase and γ-tocopherol

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methyltransferase. Overexpression of these two enzymes from *Arabidopsis thaliana* in soybean seeds greatly enhanced the conversion from δ- and γ-tocopherols to α-tocopherol, increasing the proportion of α-tocopherol from the normal 10% to >95% (Van Eenennaam et al., 2003). As a result, the transgenic soybean seeds had a 5-fold higher vitamin E activity than the untransformed seeds. By stacking up five genes involved in the tocochromanol pathway, it was possible to increase both the total content of tocochromanols and the proportion of α-tocopherol in soybean seeds (Karunanandaa et al., 2005).

Multiple vitamins

Using the approach of combinational genetic transformation (Zhu et al., 2008), Naqvi et al. (2009) produced a transgenic maize over-expressing simultaneously genes involved in the biosynthetic pathways of three different vitamins: β-carotene (pro-vitamin A), folate and vitamin C. The contents of these vitamins were increased by 169-, 2- and 6-fold, respectively, in the transgenic maize seeds compared with untransformed seeds.

Diseases resulting from western diets

Although some of the deficiencies discussed above may have impacts on populations in developed countries, or at least on specific groups of consumers within these, the major health problems associated with food in western countries result from over-consumption, and particularly over-consumption of highly refined foods which are rich in saturated fats and starch and poor in fibre. These conditions include diabetes and the "metabolic syndrome", which is characterised by resistance to insulin, hyperglycaemia, glucose intolerance, dyslipidemia (high blood triacyl glycerols and low HDL-cholesterol), central adiposity and hypertension (Alexander, 2003; Nugent, 2005; Shaw et al., 2005). Although the mechanisms determining these symptoms are not fully understood there is no doubt that increasing the consumption of fibre-rich foods with low glycaemic index at the expense of highly refined foods will have wide health benefits.

Starch

Starch and dietary fibre in cereals provide about two thirds of the total energy intake in developing countries (Cassidy, 2004), mainly from starch which comprises about 70% of the whole grain and 80% of white flour derived from wheat (the most widely consumed food grain). Starch is rapidly digested in the gastro-intestinal (GI) tract leading to rapid release of glucose with consequent rapid release of insulin, which is considered to be a major factor contributing to the development of the metabolic syndrome. The development of forms of starch which are either not digested or digested more slowly (resistant starch) is therefore a major target for plant biotechnologists and food processors. Resistant starch may also be defined as a type of dietary fibre, with benefits for colonic health (Nugent, 2005).

Starch is classically defined as a mixture of two polymers, amylose and amylopectin, both consisting of glucose residues. However, it is probable that these two polymers are not clearly defined with the distinction depending partly on the methods used (Stone and Morell, 2009). Thus, the term amylose is usually used to describe polymers comprising less than about 3000 glucose units with a very low level of α-1,6 linkages (less than 1%) compared with α-1,4 linkages and amylopectin to describe larger polymers (above about 5000 glucose units) with 3–4% α-1,6 linkages (Stone and Morell, 2009). These two polymers differ in their rate of digestion in the GI tract, with amylose being digested more slowly. Increasing the proportion of amylose has therefore been proposed as a strategy to develop resistant starch. Most plant starches comprise about 25% amylose and 75% amylopectin, with limited variation in these proportions within or between species. However, mutations in genes encoding enzymes of starch synthesis may lead to an increased proportion of amylose. A notable example is the mutant barley variety Himalaya 292, which has a reduced total content of starch (to 18% dry weight) which comprises about 70% amylose (Morell et al., 2003). Feeding trials with this line in pigs and humans showed beneficial effects including lowered plasma cholesterol but these may have resulted, at least in part, from the increase in total fibre (about 25% dry weight including 10% β-glucan) which also occurs (Bird et al., 2004; Topping et al., 2003) (discussed below). Health food products based on this line (which has been named BARLEYmax) are currently being developed in Australia. Amylose-extender mutants of maize also have increased proportions of amylose and increases in the proportion of starch which is resistant to digestion with α-amylase (from about 24% to 70%) (Evans and Thompson, 2004) and are widely use in food processing (see below).

Barley is not widely consumed as a food grain and the real challenge is to develop similar material in wheat. However, this is more difficult due to the hexaploid nature of wheat which means that many biosynthetic enzymes exist in three related forms encoded by the three genomes (in contrast barley and maize are diploid). Yamamori et al. (2000) described the combination of three natural mutations in the gene encoding the starch synthase II enzyme (which catalyses amylopectin synthesis) in wheat but the proportion of amylose was increased by less than 10%, indicating that other enzymes contribute to amylopectin synthesis would also need to be down-regulated. However, a spectacular increase to over 70% amylose was achieved by down-regulation of enzymes responsible for amylopectin branching in transgenic wheat, with feeding trials in rats showing increased indices of large bowel health (Regina et al., 2006).

These results demonstrate the feasibility of developing cereals with reduced glycaemic index but two major barriers exist to their development beyond a restricted range of health food products. Firstly, starch content is the major determinant of cereal grain yield and all mutations and transgenic events affecting starch synthesis also affect starch amount and hence grain yield and profitability. Secondly, as the major component of grain and flour, starch also affects the processing properties (including the bread making properties of wheat). This will undoubtedly pose problems for processing of wheat with substantially increased proportions of amylose but resistant starches (principally from maize) are already being incorporated into wheat bread at levels of up to about 5% in many countries (Birkett and Brown, 2008).

Dietary fibre

Dietary fibre has wide and well established health benefits, including reducing the risk of cardiovascular disease, improving glycaemia and glucose sensitivity, assisting weight management, improving bowel health and reducing the risk of certain forms of cancer (Anderson et al., 2009; Howarth et al., 2001; Slavin, 2004). In cereal diets these benefits are associated with the consumption of wholegrain products, in which the fibre-rich bran layers are retained. Thus, wholemeal wheat flour contains about 10–15% total dietary fibre compared with only 3% in white flour. The major forms of dietary fibre in cereals are non-starch polysaccharides derived from the cell wall, principally arabinoxylan (AX) and β-glucan ((1–3,1–4)-β-D-glucan) which account for about 70% and 20% of the total in wheat flour respectively (Bacic and Stone, 1980; Mares and Stone, 1973). β-glucan is of particular interest as soluble β-glucan fractions from barley and oats (where

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β-glucan is the major dietary fibre component) have benefits in reducing coronary heart disease (CHD) which have been accepted by the US FDA for health claims on food products (Anonymous, 2008).

Although the health benefits of cereal diets could be improved by increasing the proportion of wholegrain products this is difficult to achieve for several reasons, including low consumer acceptability, increased cost and adverse effects on processing quality. An alternative strategy is to select wheat varieties with higher levels of dietary fibre in their flour, particularly soluble fibre which varies in amount by over 2-fold (Ward et al., 2008). The recent identification of genes encoding β-glucan synthase in wheat and barley (Doblin et al., 2009; Nemeth et al., 2010) also provides an opportunity to increase β-glucan synthesis in wheat by transgenesis.

Plant-derived replacements for fish oils

Long chain omega-3 polyunsaturated fatty acids (LC-PUFA), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are known to have multiple beneficial effects on human health, including in neonatal growth and development (in particular brain and eye function) reducing the symptoms of the metabolic syndrome (Graham et al., 2004). LC-PUFAs cannot be synthesised by plants or animals and are traditionally consumed in fish products (and therefore referred to as fish oils) where they are actually derived from the dietary intake of microalgae and other marine microbes. Consequently, it is necessary to supplement diets for commercial aquaculture with oils extracted from non-commercial fish species, such as sand eels. The resulting depletion of fish stocks and disturbance of the marine ecosystem is neither desirable nor sustainable and alternative sources of fish oils are urgently required for aquaculture and consumers.

An attractive alternative is to synthesise LC-PUFs in plants, notably in oilseeds to replace the fatty acids which are usually stored on triacylglycerol. This approach has been taken by groups in both the plant biotechnology industry and academia, with combined proportions of up to 20% EPA and 3% DHA having been achieved despite the complexity of the system which requires the transfer of multiple rather than single genes (reviewed by Venegas-Caleron et al. (2010)). This is an impressive example of the power of transgenesis to benefit both human health and environmental sustainability.

Concluding remarks

Plant foods contribute to human health in both positive and negative ways, depending on their relative contribution to the total diet and the level of consumption. In many developing countries, and to some extent in developed countries, they provide essential mineral and micronutrients. However, over-consumption, particularly of over-refined cereal-based foods, has contributed to the development of an "epidemic" of diseases (obesity, type 2 diabetes, cardiovascular disease) which threaten the health of increasing proportions of the population in Western Europe, the USA and other developed countries.

Crop biofortification can be an important tool in fighting micronutrient malnutrition; it is complementary to, not in place of, other intervention strategies (e.g. food fortification and supplements) (Mayer et al., 2008). The main advantages of crop biofortification are the high benefit/cost ratios and that it can reach the rural poor, which is often not the case for other strategies (Mayer et al., 2008; Nestel et al., 2006; Stein, 2010). For example, the cost of breeding is estimated at about $4 million per variety spread over 10 years – representing about 0.2% of the global vitamin A supplementation expenditures (Mayer et al., 2008; Nestel et al., 2006). Where fertilizers are needed as in agronomic biofortification, the recurrent cost may deter their use in resource-poor areas, except where crop yield benefits from the fertilizer applications (e.g. Zn in deficient soils). The cost of the development and regulatory approval of a transgenic crop can be 5–10 times higher than conventional breeding, but still small compared with a classical public health intervention (Mayer et al., 2008). Poor public acceptance, especially in Europe, difficulties in getting regulatory approval or lack of biosafety regulations in target countries, and fragmented intellectual properties are hindrance to the development of nutritionally-enhanced transgenic crops (Golden Rice, for an example, Enserink, 2009; Potrykus, 2001).

This brief review has shown that it is scientifically and technically feasible to improve the nutritional value and health benefits of crops. We foresee that new crop varieties and genetically modified plants with enhanced quality, and new farming systems that accommodate more diverse crop species, can make a real impact on improving human nutrition and health over the next 20 years. Transgenesis provides opportunities to improve the nutritional quality and health benefits of plant foods for all countries and it is important that its uptake should not be stifled by a higher level of regulation than is justified on scientific grounds.

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