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Review

The genetic consequences of paternal acrylamide exposure and potential for amelioration

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ABSTRACT

Acrylamide is a toxin that humans are readily exposed to due to its formation in many carbohydrate rich foods cooked at high temperatures. Acrylamide is carcinogenic, neurotoxic and causes reproductive toxicity when high levels of exposure are reached in mice and rats. Acrylamide induced effects on fertility occur predominantly in males. Acrylamide exerts its reproductive toxicity via its metabolite glycidamide, a product which is only formed via the cytochrome P450 detoxifying enzyme CYP2E1. Glycidamide is highly reactive and forms adducts with DNA. Chronic low dose acrylamide exposure in mice relevant to human exposure levels results in significantly increased levels of DNA damage in terms of glycidamide adducts in spermatocytes, the specific germ cell stage where Cyp2e1 is expressed. Since cells in the later stages of spermatogenesis are unable to undergo DNA repair, and this level of acrylamide exposure causes no reduction in fertility, there is potential for this damage to persist until sperm maturation and fertilisation. Cyp2e1 is also present within epididymal cells, allowing for transiting spermatozoa to be exposed to glycidamide. This could have consequences for future generations in terms of predisposition to diseases such as cancer, with growing indications that paternal DNA damage can be propagated across multiple generations. Since glycidamide is the major contributor to DNA damage, a mechanism for preventing these effects is inhibiting the function of Cyp2e1. Resveratrol is an example of an inhibitor of Cyp2e1 which has shown success in reducing damage caused by acrylamide treatment in mice.

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1. Introduction

This review provides a summary of new information, building on previous reviews [1,2], on the risks of human exposure to acrylamide and the mechanisms of its action while also investigating strategies for amelioration. Acrylamide is a reproductive

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toxin which exerts its effects predominantly with exposure of males [3,4]. This exposure occurs in humans via the consumption of carbohydrate rich foods cooked at high temperatures, which produces the toxin via the Maillard reaction [5,6]. Exposure can also occur from industrial sources where polyacrylamide is used [7,8]. Polyacrylamide is ultimately contaminated with a residual amount of acrylamide monomer, allowing small levels of exposure to humans occurring in products such as grouting agents, flocculants for water treatment, and products used in the paper and cosmetics industries [8]. Acute exposure to high doses of acrylamide in male mice and rats causes a reduction in fertility in terms of reduced sperm number and quality, reduced litter sizes and an increase in DNA strand breaks and dominant lethality in offspring [9–11]. The mechanism by which acrylamide exerts these effects is as a result of the Cyp2e1 (lower case when referring to mouse homologues) mediated metabolism of acrylamide to glycidamide, a more reactive compound which is able to bind covalently to DNA [12]. Chronic exposure to acrylamide in male mice at doses relevant to human exposure has demonstrated that these glycidamide DNA adducts occur in germ cells [13]. Another window of glycidamide exposure occurs when sperm are in the epididymis, as Cyp2e1 has been demonstrated to be expressed within all three segments, with highest expression in the corpus segment of the epididymis of rats [14]. Germ cells in later stages of spermatogenesis and sperm undergoing post testicular maturation are DNA repair deficient and hence it is proposed that these lesions persist until the point of sperm maturation and downstream fertilisation [15]. This has consequences for future generations. Genetic lesions which are carried on to the offspring may lead to a genetic predisposition to diseases such as cancers [16]. Understanding the mechanism by which acrylamide exerts its toxic effects may lead to methods of reducing these effects. Inhibiting the function of the Cyp2e1 enzyme would be an ideal strategy since the reaction it catalyses is the only identified mechanism for the conversion of acrylamide to glycidamide. A number of Cyp2e1 inhibitors including diallyl sulphide, 1-aminobenzotriazole, resveratrol and other polyphenols have been investigated for their potential capacity to block the conversion of acrylamide to glycidamide and hence prevent the DNA damage caused by glycidamide adduct formation [17,18]. Antioxidants can also play a role in preventing acrylamide's toxicity. Resveratrol in particular has multiple targets and has the capacity to act as a Cyp2e1 inhibitor as well as an antioxidant [19].

2. Acrylamide production/exposure

Acrylamide has been produced since 1949 through the hydration of acrylonitrile for use in many industrial applications [20]. Its polymerised form is used widely as a filtration and flocculation aid in mining, in waste water processing, as a flow control agent in oil-well operations, as a soil stabiliser, in grouting products and in acrylamide gels used in biotechnology laboratories [8]. Polyacrylamide in these materials can contain residual amounts of contaminating acrylamide, allowing minimal exposure to humans of the monomer occurring mostly through dermal absorption and inhalation [21]. The construction of a railway tunnel in 1992 through the mountain range of Hallandsås in Sweden demonstrated the impact of industrial exposure to acrylamide [22]. A grouting agent was used to seal the tunnel, which contained acrylamide that had not polymerised properly and was leaking out of the tunnel. Large amounts of water flowed through the tunnel and downstream fish were killed and livestock found to be paralysed as a result of drinking the water. Acrylamide also leaked into the groundwater. At this time, tunnel workers and residents in the area were tested for levels of acrylamide in their blood. The acrylamide levels were assessed by measuring the haemoglobin adducts of acrylamide and glycidamide. It was determined that 160 tunnel workers had increase adduct levels from acrylamide exposure (0.07–17.7 nanomol/g Hb) [23]. Fifty tunnel workers had neurotoxic effects, of which 23 had signs of peripheral nervous system impairment out of a total of 200 workers. Levels of haemoglobin adducts were also measured in people from outside the area, as controls, and it was found that there was a background level of exposure equating to a daily intake of about 100 μg of acrylamide [24]. This was in agreement with the results of an earlier study by Bergmark [8] where adducts were found in non-smoking controls with no industrial exposure to acrylamide, with an estimated daily acrylamide intake of 0.8 μg/kg body weight (bw)/day, which equates to 56 μg/day in a 70 kg adult. At the time it was not known where this exposure to acrylamide was coming from. Levels of acrylamide found in all known sources of acrylamide at the time, including cosmetics and paper as well as tobacco smoke, were accounted for and considered to be insignificant contributors to the background levels found in control subjects. It was hypothesised that acrylamide was present in foods. Tareke et al. [5] tested this hypothesis and reported that acrylamide forms during the cooking of foods at temperatures above 120 °C. During this process, acrylamide is predominantly formed from asparagine, in the presence of reducing sugars via the Maillard reaction via Strecker type degradation [6]. Based on these findings, the Swedish National Food Administration reported that acrylamide is formed at relatively high levels in the cooking of foods including potato crisps (689–693 μg/kg), French fries (326–328 μg/kg), soft bread (27–37 μg/kg), roasted coffee (225–231 μg/kg) and breakfast cereals (132–142 μg/kg) [25]. Following this, and other studies verifying these findings, FAO/WHO reported the average acrylamide intake to be in the range of 0.3–0.8 μg acrylamide/kg bw/day for developed countries, which corresponds to about 21–26 μg/day for a 70 kg person [26]. The acrylamide present in all these sources still did not account for the high background levels (100 μg/day) found to be present in the Swedish subjects, suggesting that not all sources of acrylamide had been identified. Since this time, acrylamide has been detected in various additional foods. Different populations are ultimately exposed to varying acrylamide doses, which can be influenced by the different diets of different age groups and cultural subgroups. There is a large variation in acrylamide content with different brands and cooking processes [27,28]. Depending on personal nutritional habits, this intake level could be several fold higher. These estimates are considered conservative, with the revised estimates in 2010 being 1–4 μg/kg bw/day which equates to 70–280 μg/day for a 70 kg person [29]. In the 24th Australian Total Diet Study the levels of acrylamide in foods in Australia were reported. The average intake was determined to be 1–4 μg/kg bw/day [27]. These levels were much higher than those recommended by WHO for safe drinking water (0.5 μg/L) which corresponds to 1 μg/day for a person consuming 2 L [30]. Cigarette smoking is estimated to contribute an additional 3.1 μg acrylamide/kg bw/day [8]. Since there is now no doubt that acrylamide exposure is occurring in humans, the adverse heritable consequences of such exposure are of importance.

3. Acrylamide reactivity and genotoxicity

After oral administration in rodents, acrylamide is readily distributed and absorbed in tissues throughout the body and is proposed to be able to transit the blood testis barrier [31]. Acrylamide is an α,β-unsaturated carbonyl compound which can function as a Michaelis acceptor and undergo addition to thiol, hydroxyl or amino groups. The thiol addition is a detoxification pathway which produces acrylamide–glutathione conjugates which are excreted via the urine (Fig. 1). The process of detoxification occurs in three