Journal of Photochemistry and Photobiology B: Biology 131 (2014) 90–95

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology B: Biology

journal homepage: www.elsevier.com/locate/jphotobiol

Exposure to solar ultraviolet radiation is associated with a decreased folate status in women of childbearing age ☆

D. Borradale [a], E. Isenring [b], E. Hacker [a], M.G. Kimlin [a,*]

[a] Institute of Health and Biomedical Innovation, Queensland University of Technology, 60 Musk Ave, Kelvin Grove, QLD 4059, Australia
[b] School of Human Movement Studies, University of Queensland, St. Lucia, QLD 4072, Australia

ARTICLE INFO

Article history:
Received 29 October 2013
Received in revised form 21 December 2013
Accepted 7 January 2014
Available online 17 January 2014

Keywords:
Population study
Folate
Folic acid
Solar ultraviolet radiation
Photodegradation

ABSTRACT

In vitro studies indicate that folate in collected human blood is vulnerable to degradation after exposure to ultraviolet (UV) radiation. This has raised concerns about folate depletion in individuals with high sun exposure. Here, we investigate the association between personal solar UV radiation exposure and serum folate concentration, using a three-week prospective study that was undertaken in females aged 18–47 years in Brisbane, Australia (153 E, 27 S). Following two weeks of supplementation with 500 μg of folic acid daily, the change in serum folate status was assessed over a 7-day period of measured personal sun exposure. Compared to participants with personal UV exposures of <200 Joules per day, participants with personal UV exposures of 200–599 and >600 Joules per day had significantly higher depletion of serum folate ($p = 0.015$). Multivariable analysis revealed personal UV exposure as the strongest predictor accounting for 20% of the overall change in serum folate (Standardised $B = -0.49$; $t = -3.75$; $p = <0.01$). These data show that increasing solar UV radiation exposures reduces the effectiveness of folic acid supplementation. The consequences of this association may be most pronounced for vulnerable individuals, such as women who are pregnant or of childbearing age with high sun exposures.

1. Introduction

Folate is a vitamin that plays an essential role in one-carbon transfer reactions and DNA synthesis [1]. One carbon methylation reactions are dependent on folate for a diverse range of important molecular functions including; the synthesis of purines and pyrimidines, homocysteine metabolism and methylation of DNA, proteins and lipids; functions which are essential in cell division and metabolic processes [2]. The function of folate in these cellular processes has led to a number of hypotheses regarding the role of folate in disease aetiology. Folate deficiency is classically associated with megaloblastic (large cell type) anaemia and a particularly active area of research, with mixed outcomes, is the role of folate in the development and progression of cancerous cells (due to its essential requirement in DNA synthesis and methylation reactions) [3]. However, it is the importance of folate in the prevention of Neural Tube Defects (NTDs), such as spina bifida, where the strongest evidence exists for folate in reducing the risk of human disease [4,5]. Consequently, the need for childbearing age women to obtain adequacy in folate status is of particular importance and has been the rationale for the introduction of mandatory folic acid fortification in several countries [6].

Folate is acquired through the intake of natural folates found in foods; with rich sources including green leafy vegetables, legumes and yeast extracts, and the synthetic form, folic acid which is found in supplemental form or added as a fortificant to food [7]. Similarly to the National Institutes of Health in the United States, the National Health and Medical Research Council (NHMRC) in Australia has set the Recommended Daily Intake (RDI) for folate at 400 μg a day for adults [8,9]. Higher levels of 600 μg/day are recommended for pregnant women to reduce the risk of NTDs [9].

In vitro data show that folate and its synthetic derivative, folic acid, are both vulnerable to degradation by UVB radiation (280–315 nm), although only folic acid is vulnerable to direct degradation by the longer wavelength UVA (315–400 nm) [10]. However, only longer wavelength UVA radiation (315–400 nm) penetrates to the dermal circulation where direct impact on unmetabolised folic acid in the blood could occur [11,12]. Other processes that may impact folate status in humans include UVA exposure-derived Reactive Oxygen Species (ROS) that can oxidise the main circulatory form of folate, 5-Methyltetrahydrofolate (5-MTHF) and a

Abbreviations: FFQ, food frequency questionnaire; 5-MTHF, 5-Methyltetrahydrofolate; UV, Ultraviolet; NTDs, Neural Tube Defects; ROS, Reactive Oxygen Species.

☆ *Sources of support*: David Borradale was supported via Queensland University of Technology's Postgraduate Research Award and project costs were supported via a Queensland University of Technology's small grant award. Blackmores® supplied the folic acid supplements for the research.

* Corresponding author. Tel.: +61 7 313 85802.
E-mail address: m.kimlin@qut.edu.au (M.G. Kimlin).

1011-1344/$ - see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jphotobiol.2014.01.002

possible direct role of UV radiation in the degradation of folate in the skin, which has the potential to enhance photo and oxidative damage to folate-depleted skin cells [13–15]. For a more detailed treatment of these various mechanisms please refer to Borradale and Kimlin [16].

The impact of UV exposure on circulatory folate status in humans has not been widely investigated in population studies. Fukuwatari et al. [12] demonstrated that Japanese college students ($N = 7$) supplemented with 250 μg of folic acid per meal for two days and subsequently asked to bathe in sunlight on the third day, had a significantly reduced plasma folate status (plasma folate pre-test = 38.0 + 7.2 nmol/L vs. post-test = 28.1 + 4.6 nmol/L, $p = <0.05$). Conversely, a control group of students ($N = 7$) not supplemented with folic acid, but also asked to bathe in sunlight showed no significant depletion in plasma folate. Several other population studies have failed to observe a relationship between UV exposures and folate depletion. For example, in a controlled trial, Gambichler et al. [17] showed that participants exposed to both single and serial UVA radiation exposures via a sunbed did not have significantly lower serum folate levels to those not exposed ($N = 24$, with eight participants exposed to UVA). Several other studies have also tested the effect of multiple UVB exposures on folate status with only one of these studies, by Shaheen et al. [18] reporting significant effects on folate status in participants exposed to UVB radiation via phototherapy unit [18–21]. With UVB not able to penetrate to the dermal circulation this one significant result is surprising, however the participants in the study by Shaheen et al. [18] were vitiligo patients whose depigmentation condition may have had a role in reducing the skin's protective barrier to UV radiation. An important distinction between these studies and that by Fukuwatari et al. [12] is that none of the other studies involved the use of folic acid supplements by participants. The population evidence provided by Fukuwatari et al. [12] and lack of significant effects observed in population studies where folic acid has not been supplemented, suggests that folic acid may be the major vulnerable species of folate to degradation by UV radiation.

Thus, while there is strong *in vitro* evidence for degradation of folate by UV radiation [11–15,22,23], there remains a lack of population research in this area, with most human studies involving the use of artificial UV exposures and lacking the use of folic acid supplementation which has been shown *in vitro* to be highly vulnerable to UV radiation [12,17–21]. The hypothesis that higher solar UV radiation exposures may lead to increased degradation of circulatory folate levels for people taking folic acid supplements therefore requires further investigation. This is particularly important for women of childbearing age due to the consequences of low folate status for pregnancies. Our objective in the current study was therefore to investigate the depletion of serum folate in a sample of females of childbearing age with varying sun exposures, following a two week period of folic acid supplementation, whilst also controlling for factors such as dietary folate.

2. Methods

2.1. Study population

Healthy female participants aged 18–47 years were recruited for this study. Participants were recruited from the Brisbane area (longitude: 153 E; latitude: 27 S), Australia, through advertisements placed within a university. Volunteers were excluded if they were pregnant or attempting to conceive, less than 18 years of age, had a diagnosed malabsorptive disease such as coeliac disease, liver diseases, a history of cancer or any condition that increased sensitivity to the effects of solar UV exposure, such as an inherited photosensitivity or lupus erythematous. Participants were also instructed to cease taking folic acid supplements prior to the beginning of the study. Data collection for the project occurred during October and November 2011. All participants provided written informed consent based on the study protocol that was approved by the Queensland University of Technology (QUT) Human Research Ethics Committee (Approval no. 1100000933).

2.2. Study design and measures

In this three week longitudinal study, participants were supplemented with a 500 μg folic acid supplement daily for two weeks. After the two weeks of supplementation, serum folate was measured as a baseline measure, followed by a second serum folate measurement after one week of personal sun exposure measurements. The outcome variable for this investigation was the change in serum folate, between these two time points. A 500 μg folic acid supplement was chosen due to this being the level of periconceptional folic acid supplementation recommended by the NHMRC for childbearing age women planning a family [24]. The supplement was supplied by Blackmores Limited and is a listed product on the Australian Register of Therapeutic Goods (ID: 118091). The length of folic acid supplementation was chosen based on prior research showing significant increases in serum folate status following two weeks supplementation [25].

Dietary intake of folate was determined through the use of a validated food frequency questionnaire [26]. General health information, usual physical activity, use of supplements, and medication usage was collected at the beginning of the study using a general health and information questionnaire. The questions used in the general health and information questionnaire have been used in previous research undertaken in the AusD study (27). Due to alcohol's influence on folate status, a question was also included assessing participants usual intake of alcohol [28]. Additionally, participants were asked whether alcohol intake, medication or supplement usage had changed from that indicated in the general health information questionnaire over the course of the study.

Body Mass Index (BMI) was measured at the beginning of the study using a standard portable stadiometer (S + M) and rounded to the nearest cm. Weight was recorded to the nearest kg and was measured using a set of electronic scales placed on a hard surface. Measurement error was minimised with the use of the same set of scales and stadiometer for all measurements in the sample. Inter-rater bias was eliminated by the use of a single observer for all measurements who was trained in the anthropometric measurement of subjects.

2.3. Personal sun exposure assessment

A seven day sun exposure and physical activity diary was provided to participants for self-completion each day. Participants reported the time spent outside in the sun in 15-min intervals for each hour of the day between 5 am and 7 pm. The use of sunscreen, clothing worn and level of physical activity were also assessed during this time. The sun exposure and physical activity diary has been used previously for sun exposure research in populations, most recently in the AusD study [27]. Environmental UV radiation was measured with a Solar Light Co., 501A biometer, located at the AusSun Research Laboratories at QUT Kevin Grove campus. The detector collects solar UV data in 5-min intervals and reports the exposure as J/m^2. Participants were physically located within a 25 km radius of this detector thus all were exposed to similar environmental UV radiation.

Participants' self-reported time in the sun (collected from the sun exposure diary) was combined with environmental UV data