Saturated Fatty Acid Intake Is Associated With Increased Inflammation, Conversion of Kynurenine to Tryptophan, and Delta-9 Desaturase Activity in Healthy Humans

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ABSTRACT: Saturated fat ingestion has previously been linked to increases in inflammation. However the relationship between saturated fatty acid (SFA) intake and the kynurene:tryptophan ratio (\([\text{Kyn}]:[\text{Trp}]\)) has not yet been investigated. This study evaluated in healthy, middle aged, individuals (men = 48, women = 52), potential relationships between SFA intake, red blood cell (RBC) membrane SFAs and monounsaturated fatty acids (MUFA), the \([\text{Kyn}]:[\text{Trp}]\) ratio, C-reactive protein (CRP), TNF-\(\alpha\) and \(\Delta^9\) desaturase activity. 

\([\text{Kyn}]:[\text{Trp}]\) was positively associated with increases in Total fat \((P = .034)\) intake, including Total SFA \((P = .029)\) and Total MUFA \((P = .042)\) intakes. Unexpectedly the \([\text{Kyn}]:[\text{Trp}]\) ratio was inversely associated with the percentage of Total RBC SFAs \((P = .004)\) and positively associated with percentage of Total MUFA \((P = .012)\) present in the RBC membrane. We found a positive association between \(\Delta^9\) desaturase activity, responsible for the desaturation of various SFAs to MUFAs, and \([\text{Kyn}]:[\text{Trp}]\) \((P = .008)\). \([\text{Kyn}]:[\text{Trp}]\) was also positively associated with CRP \((P = .044)\), however no significant relationship between \([\text{Kyn}]:[\text{Trp}]\) and TNF-\(\alpha\) was found. This study shows for the first time that SFA consumption increases inflammatory pathways linked to increased tryptophan to kynurenine conversion, even in healthy humans. Our data also suggests that SFA linked increases in inflammation occur concomitantly with an-upregulation of \(\Delta^9\) desaturase activity resulting in increased desaturation of SFA substrates to their MUFA derivatives.

KEYWORDS: Indoleamine 2,3 dioxygenase (IDO), tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), diet, oleic acid, stearic acid.

Introduction

Excessive intake of saturated fatty acids (SFA) is associated with several disease states including cardiovascular disease, diabetes and certain types of cancer.¹-³ While multiple processes are implicated, a key mechanism by which SFAs have been shown to drive disease is through increasing the activity of inflammatory pathways. Indeed increased SFA intake has been repeatedly correlated with increased tissue and/or serum cytokine levels in humans.⁴,⁵ While further research is required to confirm the processes involved, both direct and indirect mechanisms have been implicated. Indirectly SFA intake stimulates postprandial as well as longer term inflammation by increasing the expression of proinflammatory genes.⁶-⁹ Following ingestion, SFAs have also been found to initiate an innate immune response by both promoting the translocation of endotoxins such as lipopolysaccharide (LPS) from the gut into circulation and by increasing the differentiation and proliferation of T helper 1 (Th1) and Th17 cell populations within the small intestine.⁹,¹⁰

In addition to these multi-step processes evidence suggests that SFAs also promote inflammation directly by activating toll-like receptor (TLR) 2/4. Through this mechanism, SFAs are thought to drive cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NF-κB) mediated production of proinflammatory cytokines, such as TNF-\(\alpha\).⁸,¹¹-¹³ However the direct activation of TLRs by SFA is contentious. Recent research suggests that while TLRs do regulate SFA induced inflammation,¹⁴ this may be because SFA upregulate TLRs that have already been primed, by LPS for example.¹³,¹⁴ Regardless of the precise mechanism involved, there is strong evidence that SFA ingestion upregulates innate immune activity.

Interferon gamma (IFN-\(\gamma\)) is a cytokine secreted by a number of innate immune cells including the Th1 subtype. Its mRNA levels have been shown to increase in murine models following chronic SFA ingestion.¹⁵ Importantly IFN-\(\gamma\) induces the transcription of indoleamine 2,3 dioxygenase (IDO), thereby modulating catabolism of the low abundance amino acid tryptophan (Trp). Induction of IDO results in reduced T-cell activation and proliferation, through negative feedback mechanisms,¹⁶ as well as an increase in the breakdown of Trp to kynurenine (Kyn).

Accordingly the ratio of Kyn to Trp concentrations ([Kyn]:[Trp]) has been widely utilised as an indirect measure of IDO and consequently IFN-\(\gamma\) mediated inflammatory activity.¹⁷,¹⁸ However, despite the demonstrated association between SFAs and increased inflammation, the effect of SFA intake on [Kyn]:[Trp] has not yet been investigated.
To better understand this relationship we therefore explored, in an essentially healthy cohort, potential relationships between; the plasma [Kyn]:[Trp] ratio and fatty acid (FA) intake, RBC membrane FA levels and Δ9 desaturase activity (a key player in human cell membrane lipid metabolism). We also measured plasma C-reactive protein (CRP) and TNF-α concentrations as additional markers of inflammation.

Methods
Participants
This cross-sectional study included 100 participants (48 males and 52 females) aged between 40 and 75 years. Participant recruitment was conducted at the Sydney Adventist hospital, and the University of New South Wales, Sydney, via advertisements on the hospital/university intranet. Participant mean BMI, visceral fat mass and blood pressure are presented in Table 1. Participants were in general good health, non-smokers, and did not have a known microbial infection, suffer from any form of neurodegenerative disease, medically diagnosed liver or kidney disorder, or inflammatory bowel disease. Participants had not been diagnosed with cancer or treated for cancer and had not undergone major surgery in the past 2 years. In the 2 weeks prior to testing participants had not taken antibiotics, illicit drugs, supplements or any complementary medicines and did not currently taking any diabetic, thyroid or anti-inflammatory medications. After obtaining written informed consent, participants were asked to complete a dietary questionnaire to assess their fatty acid intake. Blood was performed in a fasted state (about 12 hours) on the same day as the completion of the questionnaire. Ethical approval for the study was obtained from the Adventist HealthCare Limited Human Research Ethics Committee, Sydney Adventist Hospital, Australia (HREC number: 2013-022).

Plasma kynurenine and tryptophan
Plasma kynurenine (Kyn) and tryptophan (Trp) levels were measured using high-performance liquid chromatography (Shimadzu LC-10AVP system, equipped with SPD-10A UV detector, Kyoto, Japan), as previously described. The [Kyn]:[Trp] ratio was calculated by dividing the concentration of Kyn by the concentration of Trp.

Fatty acid (FA) intake
Self-report average daily fatty acid intake (g/day) was assessed using the Cancer Council Victoria Dietary Questionnaire for Epidemiological Studies Version 2 (DQES v2). This questionnaire asks participants to report their usual consumption of 74 foods and 6 alcoholic beverages over the preceding 12 months using a 10-point frequency scale. Additional questions are included about the type, number and serving size of fruit, vegetables, bread, dairy products, eggs, fat spreads and sugar. Fatty acid intakes were computed from NUTTAB 2010 and AUSNUT 2007, national government food composition databases, using software developed by the Cancer Council of Victoria. However the intake of Vaccenic acid could not be quantified. Both the development of the DQES and its validation in Australian adults have been previously reported.

RBC membrane fatty acids
The fatty acid composition of red blood cells (RBC) was determined using a modified method originally developed by Lepage and Roy (1986). Briefly sample fatty acids were methylated by the addition of 200 μl of acetyl chloride followed by heating at 100°C for 1 hour. About 5 ml of 6% K2CO3 solution was added to stop the reaction. The samples were then centrifuged at 3000 × g for 10 minutes and the supernatant containing the fatty acid methyl esters was transferred into glass vials. Fatty acid methyl esters were quantified using a Hewlett Packard 6890 Gas Chromatograph equipped with a...
flame ionisation detector. The identity of each fatty acid peak in the sample was determined by comparing the peaks retention time with the retention time of synthetic standards of known fatty acid composition. Fatty acid results are reported as percentage of total fatty acids.

$\Delta^9$ Desaturase ($\Delta^9$) activity

$\Delta^9$ Desaturase ($\Delta^9$) activity was estimated by calculating the ratio of membrane Oleic acid (C18:1(n-9)) to membrane Stearic acid (C18:0).

Statistical analysis

Biochemical and dietary intake data were integrated using SPSS version 25.0 for Windows. Outliers classified as $3 \pm$ standard deviations from the mean were removed. Normality was assessed using both the Shapiro-Wilk and Kolmogorov-Smirnov tests. Histogram displays were also visualised. When required Box-Cox or log transformations were performed. Multiple linear regression controlling for age and gender was undertaken to assess associations between the [Kyn]/[Trp] ratio, CRP, TNF-α, the percentage of RBC membrane fatty acids and fatty acid intake. Normality of the standardised residuals was assessed by examining histograms and P-P plots. Scatter plots of the residuals were also assessed to confirm homoscedasticity. All Tolerance values were greater than 0.01 and all Variance Inflation Factors (VIF) were less than 10. R-squared ($R^2$) values and standardised coefficients ($\beta$) are provided throughout. Pearson’s correlation was used to determine associations between individual fatty acids, both membrane and diet derived. The $r$ value is provided. Associations were considered significant when $P \leq .05$.

Results

Relationships between plasma [Kyn]:[Trp] ratio and FA intake

Mean levels of kynurenine, tryptophan, the [Kyn]:[Trp] ratio and daily intake of fatty acids are presented in Table 2. We observed a significant positive association between the [Kyn]:[Trp] ratio and Total fat intake ($n = 98$, $R^2 = 0.152$, $\beta = 0.210$, $P = .034$) including Total MUFA ($n = 98$, $R^2 = 0.148$, $\beta = 0.199$, $P = .042$) and Total SFA ($n = 98$, $R^2 = 0.154$, $\beta = 0.218$, $P = .029$).

Although not significant, an increase in the [Kyn]:[Trp] ratio also tended to be related to an increased intake of both Palmitic ($n = 98$, $R^2 = 0.140$, $\beta = 0.179$, $P = .073$), Stearic ($n = 98$, $R^2 = 0.143$, $\beta = 0.188$, $P = .059$) as well as Arachidic ($n = 98$, $R^2 = 0.134$, $\beta = 0.159$, $P = .110$) saturated fats.

An increased intake of Oleic acid also tended to be associated with an increase in the [Kyn]:[Trp] ratio, although this was not statistically significant ($n = 96$, $R^2 = 0.137$, $\beta = 0.171$, $P = .089$). No association between the [Kyn]:[Trp] ratio and the intake of Palmitoleic ($n = 96$, $R^2 = 0.114$, $\beta = 0.066$, $P = .505$) or Gondoic ($n = 97$, $R^2 = 0.107$, $\beta = 0.045$, $P = .657$) MUFAs were observed. The intake of Vaccenic acid was not quantified.

Relationship between plasma [Kyn]:[Trp] ratio and RBC membrane FA levels

Unexpectedly we observed a significant inverse association between the [Kyn]:[Trp] ratio and the percentage of Total SFA incorporated into the RBC membrane ($n = 98$, $R^2 = 0.186$, $\beta = -0.286$, $P = .004$). In particular an increase in the [Kyn]:[Trp] ratio was found to be significantly associated with a reduction in the percentage of Stearic acid in the cell membrane ($n = 98$, $R^2 = 0.158$, $\beta = -0.224$, $P = .023$) and a non-significant reduction in the percentage Palmitic ($n = 98$, $R^2 = 0.123$, $\beta = -0.116$, $P = .240$) as well as Arachidic acid ($n = 98$, $R^2 = 0.120$, $\beta = -0.102$, $P = .296$).

We also observed a positive association between the [Kyn]:[Trp] ratio and the percentage of Total MUFAs incorporated into the membrane ($n = 98$, $R^2 = 0.168$, $\beta = 0.243$, $P = .012$). Specifically a significant positive association between the [Kyn]:[Trp] ratio and the membrane percentage of Palmitoleic ($n = 98$, $R^2 = 0.164$, $\beta = 0.237$, $P = .015$) as well as Oleic acid ($n = 98$, $R^2 = 0.161$, $\beta = 0.227$, $P = .019$) was observed. No associations between the [Kyn]:[Trp] ratio and the percentage of Vaccenic ($n = 98$, $R^2 = 0.112$, $\beta = 0.05$, $P = .623$) or Gondoic ($n = 97$, $R^2 = 0.113$, $\beta = -0.059$, $P = .551$) acid was found. The mean membrane percentages of FAs are presented in Table 2.

Correlation between dietary FA intake and RBC membrane FA levels

Of some surprise the dietary intake of Palmitic acid was not correlated with the percentage of membrane Palmitic ($n = 100$, $r = 0.006$, $P = .952$) or Palmitoleic ($n = 100$, $r = 0.003$, $P = .980$). An increase in Palmitic acid tended to be linked to a decrease in Vaccenic acid ($n = 100$, $r = -0.145$, $P = .115$) however this was not statistically significant.

While the intake of Stearic acid was not correlated with the percentage of membrane Stearic acid ($n = 100$, $r = 0.049$, $P = .626$), a significant positive correlation between the intake of Stearic acid and the percentage of Oleic acid in the membrane was noted ($n = 100$, $r = 0.203$, $P = .043$). No correlation between Stearic acid intake and membrane Gondoic acid was observed, although the trend appeared to be inverse ($n = 100$, $r = -0.066$, $P = .515$).

The intake of Arachidic acid did not correlate with the percentage of Arachidic acid within the membrane ($n = 100$, $r = 0.095$, $P = .348$). Likewise the intake of Palmitoleic ($n = 98$, $r = 0.032$, $P = .755$), Oleic ($n = 98$, $r = 0.126$, $P = .218$) and Gondoic acid ($n = 99$, $r = -0.025$, $P = .803$) did not correlate with the corresponding percentage of FAs in the membrane.
Correlation between dietary intake of total SFA and MUFA

We found that the intake of total SFAs significantly influenced the intake of MUFAs (n = 100, \( R^2 = 0.733, \beta = 0.886, P = .000 \)). A 1 g/day increase in SFA intake was linked to a 0.886 g/day increase in MUFA intake.

Correlations between individual RBC membrane FA levels

We then sought to determine the relationship between RBC membrane SFAs and their MUFA derivatives. An increase in the percentage of Palmitic acid within the membrane was significantly correlated with an increase in Palmitoleic (n = 100,
This was not statistically significant (n = 97, TNF-α levels tended to rise alongside the [Kyn]:[Trp] ratio (n = 91, r = .243). P = .000) but not Vaccenic acid (n = 100, r = .029, P = .777).

While increased cell membrane levels of Stearic acid were correlated with a significant decrease in the percentage of its derivative Oleic acid (n = 100, r = -.572, P = .000), a positive correlation between the percentage of Stearic acid and Gondoic acid was observed (n = 100, r = .482, P = .000). MUFA derivatives of Arachidic acid were not quantified.

Association between Δ9 desaturase activity, the [Kyn]:[Trp] ratio and other markers

To further understand the relationship between membrane fatty acid levels and the [Kyn]:[Trp] ratio we estimated Δ9 desaturase (Δ9) activity by calculating the ratio of product (membrane Oleic acid; C18:1(n-9)) to substrate (membrane Stearic acid; C18:0). Using this method we observed a significant positive association between Δ9 desaturase activity and the [Kyn]:[Trp] ratio (n = 97, R² = 0.096, β = 0.282, P = .008). An increase in Δ9 activity also tended to be associated with an increase in [TNF-α] (n = 99, R² = 0.052, β = 0.177, P = .090), however this was not statistically significant. Δ9 desaturase activity was not associated with [CRP] or the intake of Total fats, including Total MUFA and Total SFA intake.

Relationship between inflammatory markers and the [Kyn]:[Trp], FA intake and RBC membrane percentages

We observed a significant positive association between concentrations of the acute phase, inflammatory marker CRP and the [Kyn]:[Trp] ratio (n = 91, R² = 0.168, β = 0.203, P = .044). While TNF-α levels tended to rise alongside the [Kyn]:[Trp] ratio this was not statistically significant (n = 97, R² = 0.124, β = 0.118, P = .243).

A significant positive association was also observed between plasma [CRP] and the percentage of membrane Palmitic (n = 93, R² = 0.078, β = 0.256, P = .015) and Palmitoleic acid (n = 93, R² = 0.098, β = 0.296, P = .005) as well as Total MUFA (n = 93, R² = 0.061, β = 0.217, P = .039). No associations between [CRP] and the percentage of membrane Stearic, Arachidic, Oleic or Gondoic acid or Total SFAs were found.

CRP was not associated with the intake of Total fats, including Total MUFA and Total SFA. Similarly the intake of Palmitic, Stearic and Arachidic acid as well as Palmitoleic, Oleic or Gondoic acid were not associated with CRP concentrations.

No significant associations were observed between plasma [TNF-α] and FA intake or membrane percentages. Mean levels of inflammatory markers are presented in Table 2.

Discussion

Substantial evidence has accumulated in recent years indicating that the ingestion of SFA increases innate immune activity resulting in both a postprandial and, with regular intake, chronic rise in pro-inflammatory mediators; see Zhou et al for a recent review.22 Despite this, the association between the ingestion of SFA and the [Kyn]:[Trp] ratio, a marker of INF-γ mediated inflammatory processes, had not been previously reported. We therefore investigated, in an essentially healthy cohort, whether the intake of fatty acids and their percentage within the membrane influence the ratio of Kyn to Trp in plasma.

As expected we observed a significant positive association between the [Kyn]:[Trp] ratio and Total fat intake, including total SFA intake. Looking at individual fatty acids we noted that, although not statistically significant, an increase in the intake of Palmitic, Stearic as well as Arachidic saturated fats tended to correspond to a rise in [Kyn]:[Trp]. As previously discussed SFA ingestion has been shown to increase the activity and/or concentration of pro-inflammatory mediators via activation of innate immune pathways. Specifically the consumption of a high fat diet, rich in SFAs, has been shown in marine models to increase the gene expression and concentration of INF-γ, resulting in the upregulation of IDO.21 As IDO is the rate-limiting enzyme responsible for catabolism of Trp to Kyn, increased IDO activity in response to SFA induced inflammation is consistent with our findings. This is further evidenced by the positive association we observed between the acute phase inflammatory marker CRP and the Δ9 desaturase activity by calculating the ratio of product (membrane Oleic acid; C18:1(n-9)) to substrate (membrane Stearic acid; C18:0). Using this method we observed a significant positive association between Δ9 desaturase activity and the [Kyn]:[Trp] ratio (n = 97, R² = 0.096, β = 0.282, P = .008). An increase in Δ9 activity also tended to be associated with an increase in [TNF-α] (n = 99, R² = 0.052, β = 0.177, P = .090), however this was not statistically significant. Δ9 desaturase activity was not associated with [CRP] or the intake of Total fats, including Total MUFA and Total SFA intake.

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derivative, as well as the known influence of SFAs and MUFAs on inflammatory activity, we hypothesised that these observations may be due to an increase in the activity of Δ9 desaturase (also called Stearoyl-CoA 9-desaturase). Δ9 desaturase is the rate limiting enzyme responsible for the desaturation of both Palmitic and Stearic acid to Palmitoleic and Oleic acids respectively (Figure 1).

Consistent with this hypothesis, the activity of Δ9 desaturase was positively associated with the [Kyn]:[Trp] ratio. Δ9 desaturase activity also tended to rise alongside increases in TNF-α. Importantly TNF-α has been shown to transcriptionally enhance IFN-γ induced IDO expression,28 thus facilitating the catabolism of Trp to Kyn. In accordance with this we also observed a parallel, though not statistically significant, rise in [TNF-α] alongside the [Kyn]:[Trp] ratio. Others have similarly reported positive associations between Δ9 desaturase activity and both circulating SFAs and inflammatory markers in humans.29

Thus considered as a whole, the data suggests that stimulation of innate immune pro-inflammatory processes, in response to chronic SFA ingestion, upregulates Δ9 desaturase activity resulting in increased desaturation of SFA substrates (eg, Stearic and Palmitic acid) to their MUFA derivatives.30 This goes some way to explain the initially unexpected findings of an inverse correlation between [Kyn]:[Try] and RBC membrane SFAs and yet positive correlation between [Kyn]:[Try] and the MUFAs, (being the corresponding SFA metabolites of Δ9 desaturase activity). While lower SFA intake has demonstrated benefits,31 reduced membrane concentrations due to desaturation may have an opposing effect.30 Indeed increased Δ9 desaturase activity, expression or concentration, has previously been associated with several disease states including Alzheimer’s disease,32 diabetes,31 and some forms of cancer.34,35 The high degree of Δ9 desaturase regulation indicates that maintaining cellular lipid homeostasis is likely vital for a variety of cellular processes, with either too much or too little saturated or mono-unsaturated FAs having detrimental consequences.36-39

This study did have a number of limitations. While the method of estimating Δ9 desaturase activity in cell membranes was sound, and previously used by others,40 we did not directly quantify Δ9 desaturase activity. As such the present results for Δ9 desaturase activity should be interpreted with caution pending future confirmation using direct measurements. Similarly while the [Kyn]:[Try] ratio is commonly used as a surrogate indicator of INF-γ induced IDO activity, both INF-γ and IDO activity were not directly measured. A number of the reported observations also did not quite reach statistical significance. However none of these observations were solely relied upon in the formation of assumptions or conclusions, and only reported as a ‘trend’ when the effect size was appropriately robust. Future studies involving a larger number of participants that directly quantitates levels of INF-γ and both Δ9 desaturase and IDO activity should however be performed to confirm our findings. Investigations using cell culture and/or animal models should also be undertaken to elucidate the mechanisms involved.

Despite these limitations, a number of conclusions can be reliably drawn from this study. The data confirms reports by others of a parallel rise in inflammation alongside chronic SFA consumption, even in healthy humans. A unique finding from this data was that SFA intake increases kynurenine production from tryptophan, most likely through stimulation of IDO activity via INF-γ mediated pathways. In addition, while awaiting confirmation with direct testing, our data suggest that SFA

Figure 1. Fatty acids synthesis.

Increased ingestion of saturated fatty acids, in particular Palmitic acid (C16:0) and Stearic acid (C18:0) may cause upregulation of delta 9 desaturase (Δ9) via an increase in indoleamine 2,3 dioxygenase (IDO) mediated inflammation. This may result in increased conversion of saturated fatty acids to their monounsaturated derivative.
linked increases in inflammatory activity concomitantly with an upregulation of Δ9 desaturase activity resulting in increased desaturation of SFA substrates to their MUFA derivatives. Due to the role of inflammation in the development and progression of several disease states we hope these findings can increase the awareness of health professionals to the probability that SFA consumption will accelerate tryptophan catabolism via the kynurenine pathway creating a range of negative health sequelae. 41

Author's Note
All authors read and approved the final manuscript.

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Author Contributions
JB, RG: conceptualisation; JB: ethics; JB, RG: data analysis; JB, CS, NB, CT: biochemical analysis; RG: funding acquisition; JB, NS: logistics; RG: supervision; JB, RG: writing original draft; NS, NB, CS, CT: writing – review and editing.

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