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Circulating antioxidant defences are decreased in healthy people after a high-fat meal

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The aim of this study was to examine the responses of uric acid, antioxidant defences and pro-oxidant variables after a high-fat meal. Twenty-five healthy persons without criteria for the metabolic syndrome, underwent a high-fat meal with Supracal® (60 g fat). Measurements were made at baseline and 3 h after the meal of TAG, uric acid, HDL-cholesterol, total proteins and oxidative stress. Following the high-fat meal, we detected a significant increase in pro-oxidative variables and a decrease in antioxidative variables. The uric acid concentrations were significantly lower after the high-fat meal and the reduction correlated significantly with the oxidative stress variables. The inverse relation between reduced uric acid and increased carbonylated proteins remained in multiple regression analysis. We conclude that uric acid is a powerful antioxidant and its reduction following a high-fat meal may be related with its acute antioxidative action.

Uric acid: Oxidative stress: Postprandial hyperlipidaemia: High-fat meal

The increase in TAG after fat intake is defined as postprandial hyperlipidaemia. Clinical studies have shown that increased postprandial concentrations of TAG are associated with coronary and arterial disease[1,2] and with insulin resistance[3]. Studies in healthy volunteers have shown that postprandial hyperlipidaemia causes a marked increase in oxidative stress and a worsening in endothelial function[4]. Postprandial lipoproteins, especially chylomicrons and VLDL, appear to generate oxygen radicals on the endothelial surface that react with nitric oxide and reduce its availability[5].

Our group has previously detected a close association between TAG and uric acid concentrations. Hypertriacylglycerolaemia due to increased levels of VLDL is associated with hyperuricaemia with reduced renal excretion of urates[6,7] and the connection between hyperuricaemia and hypertriacylglycerolaemia has a genetic association[8,9].

Many questions remain concerning hyperuricaemia. Current debate is centred on whether high concentrations of uric acid represent a marker of cardiovascular risk or a cardiovascular risk factor itself. This debate is fuelled by the paradoxical effect of purine metabolism on oxidative stress; on one hand the action of xanthine oxidase on xanthine produces uric acid and superoxide radicals belonging to the reactive oxygen species[10], and on the other, uric acid is an abundant aqueous antioxidant that accounts for almost two-thirds of all free-radical scavenging activity in human serum[11]. Allantoin, formed from the non-enzymatic oxidation of urate, is a marker of the antioxidative effect of uric acid[12].

In short, we know that a high-fat meal is accompanied by an increase in oxidative stress but we do not know the clinical importance of the concentration of uric acid or whether its antioxidative ability plays any part in the oxidative damage resulting from a high-fat meal. Accordingly, the main aim of the present study was to determine the association between uric acid and the increase in oxidative stress following a high-fat meal in healthy persons.

Material and methods

We selected twenty-five healthy persons who were accompanying patients on primary care visits, thirteen men and twelve women. These persons, who all had a normal oral glucose tolerance test and had experienced no change in weight over the previous 3 months, consumed a 60 g high-fat meal with a commercial liquid preparation (Supracal®; SHS International, Liverpool, UK). Only water was permitted during

Abbreviations: GSH-Px, glutathione peroxidase; GSH-Rd, glutathione reductase; NOx, total nitrites (nitrites and nitrates).

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the process, and no physical exercise was undertaken. The commercial preparation of 125 ml contains 60 g fat, of which 12 g are saturated, 35·35 g are monounsaturated, and 12·75 g are polyunsaturated. Each 100 ml contains < 1 g lauric acid, < 1 g myristic acid, 4·8 g palmitic acid, 1·4 stearic acid, 27·7 g oleic acid, 9·6 g linoleic acid, 1·4 behenic acid, and 0·5 g lignoceric acid.

Blood samples were obtained from the antecubital vein and placed in chilled vacutainer tubes (BD vacutainer™, London, UK). The serum was immediately separated by centrifugation for 30 min at 956 rpm and frozen at −80°C until analysis. The study protocol was approved by the local Bioethics Committee. All subjects gave informed consent to the study, which was approved by the Ethics Committee of Virgen de la Victoria Clinical University Hospital.

Variables evaluated

Measurements were made in all subjects of age (in years), weight, height (to calculate the BMI, calculated as the weight (kg) divided by the height squared (m^2)), and waist and hip circumferences (to calculate the waist:hip ratio, calculated as the waist circumference divided by the hip circumference)[13]. Measurements and corresponding calculations were made in serum samples of glucose, total protein, uric acid, cholesterol, TAG, HDL-cholesterol, apoAI, apoB, creatinine, C-reactive protein, as well as 24 h uric acid urinary excretion. Additionally, at 3 h, measurements were made of cholesterol, TAG, apoB, uric acid, and pro-oxidant and antioxidant variables. The measurements were made with a Dimension autoanalyser from Dade Behring Inc. (Deerfield, IL, USA). Additionally, insulin and dehydroepiandrosterone sulphate levels were quantified by RIA provided by BioSource S.A. (Nivelles, Belgium) and Beckman Coulter Inc. (Fullerton, CA, USA), respectively.

Lipid peroxidation products (malondialdehyde + 4-hydroxyalkenals) and glutathione reductase (GSH-Rd) activity were estimated using reagents purchased from Oxis International (Portland, OR, USA), i.e. LPO-586 and GR-340 kits, respectively. Additionally, glutathione-*S*-transferase activity was evaluated using reagents purchased from BioVision Inc. (Mountain View, CA, USA), i.e. GST Colorimetric Activity Assay kit.

The protein carbonyl content was evaluated using the method of Levine *et al.* [14]. Total nitrites (nitrites and nitrates; NOx) was used as a marker of nitric oxide (NO) levels and assayed following the Griess method[15] in serum. Glutathione peroxidase (GSH-Px) activity was evaluated by the Flohé and Gunzler method[16], whereas catalase and total superoxide dismutase activities were assayed following the Aebi technique[17] and Marklund method[18], respectively. The CV of the techniques were less than 10 %.

Statistical analysis

Pearson correlations were made between study variables in order to evaluate their association. Comparisons between experimental conditions (baseline versus after high-fat meal) were determined using a paired-sample test (Wilcoxon). A multiple regression analysis was done to study the associations between the variables that correlated. In all cases the rejection level for a null hypothesis was a $P=0{\cdot}05$ for two tails. Calculations were performed with SPSS software (version 11.0; Statistical Package for the SPSS Iberica, Madrid, Spain).

Results

Table 1 shows the characteristics of the study subjects; none of them fulfilled the Adult Treatment Panel III criteria for the metabolic syndrome.

Table 2 shows the associations between the oxidative stress measurements and the levels of uric acid and TAG prior to the high-fat meal. The baseline levels of plasma TAG were inversely correlated with the antioxidant variables: GSH-Rd, glutathione-*S*-transferase and superoxide dismutase (r −0·57, r −0·60, r −0·64, respectively), and directly with the oxidant variables: NOx, lipid peroxidation and carbonylated proteins (r 0·74, r 0·49, r 0·55, respectively). Moreover, as well as a strong inverse association between NOx and GSH-Rd (r −0·76), strong correlations were found between oxidant variables and antioxidant variables (Table 2).

Table 3 shows the comparison of the means of those variables studied both before and after the high-fat meal. There was a significant increase in the values of TAG, lipid peroxidation, carbonylated proteins, and a significant reduction in GSH-Px, GSH-Rd, NOx and plasma uric acid after the high-fat meal.

Table 4 shows the correlations of the differences in the variables before and after the high-fat meal. There was a negative association between the difference in the plasma levels of uric acid and the glutathione-*S*-transferase and a positive correlation with the carbonylated proteins (r −0·59, r 0·74, respectively).

Finally, Table 5 shows a multiple regression analysis of the difference in the plasma uric acid levels according to the other variables studied. The increase in the levels of carbonylated proteins after the high-fat meal was the only variable that predicted significantly the variance of this difference in uric acid levels.

Table 1. Baseline biological characteristics of the study subjects

	Mean	SD
Sex (male/female)	13/12	
Age (years)	39·5	11·25
Waist to hip ratio	0·878	0·073
Waist circumference (cm)	88·95	10·02
Systolic blood pressure (mmHg)	110	8·1
Diastolic blood pressure (mmHg)	72	7·3
Cholesterol (mmol/l)	5·53	1·21
TAG (mmol/l)	0·94	0·32
HDL-cholesterol (mmol/l)	1·61	0·45
Baseline glucose (mmol/l)	4·96	0·40
ApoAI (mg/dl)	175·16	41·29
ApoB (mg/dl)	117·94	27·27
Baseline insulin (μU/ml)	9·67	4·14
Fractional excretion of uric acid (%)*	7·90	2·44
BMI (kg/m^2)	25·37	3·00
LDL-cholesterol (mmol/l)	3·27	0·79
Uric acid (μmol/l)	299·77	57·10

*Calculated as: (urinary uric acid × serum creatinine)/(serum uric acid × urinary creatinine) × 100.

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Table 2. Correlations of the baseline values of the variables in the study subjects†

	Uric acid	TAG	GSH-Px	GSH-Rd	GST	SOD	NOx	LPO	ProCar
TAG	0·27								
GSH-Px	0·422	−0·249							
GSH-Rd	−0·063	−0·571*	0·192						
GST	0·150	−0·609*	0·176	0·788*					
SOD	0·159	−0·645*	0·244	0·371	0·343				
NOx	0·168	0·741*	−0·304	−0·760*	−0·696*	−0·608*			
LPO	0·281	0·499*	−0·111	−0·769*	−0·667*	−0·391	0·890*		
ProCar	0·039	0·558*	−0·133	−0·666*	−0·553*	−0·619*	0·850*	0·746*	
CAT	−0·075	0·107	0·042	−0·411	−0·639*	−0·146	0·371	0·565*	0·277

Correlations were significant: *$P<0·05$.

†Antioxidant defence variables: CAT, catalase; GSH-Px, glutathione peroxidase; GSH-Rd, glutathione reductase; GST, glutathione-*S*-transferase; SOD, superoxide dismutase. Marker of vasodilatations: NOx, total nitrites (nitrites and nitrates). Pro-oxidant variables: LPO, lipid peroxidation; ProCar, protein carbonyl.

Discussion

The results of the present study show that a high-fat meal in healthy persons produces an increase in the plasma levels of postprandial TAG and generates strong oxidative stress, because circulating antioxidant defences were decreased.

The association between plasma TAG levels and oxidative stress variables is known, as an accumulation of TAG and an intracellular increase in fatty acids produces an increase in cell catabolism and a release of electrons in the mitochondria, with the resulting increase in free radicals[19]. This increase in free radicals provokes a rise in oxidation and activates the antioxidant mechanisms of the organism. The increased oxidative variables after a high-fat meal and the inability of the antioxidant defences of the organism to detain this increase is known as postprandial oxidative stress[20,21]. Oxidative stress has been involved in the pathogenesis of CVD and in the genesis of the metabolic syndrome[22]. Moreover, oxidative stress that accompanies postprandial lipidaemia can modify the endothelial function[4]. In the present study we found an inverse association between the antioxidant defences of the organism and the plasma levels of TAG, even under fasting conditions, and that a high-fat meal results in an important increase in lipid peroxidation and carbonylated proteins and a decrease in both GSH-Px and GSH-Rd activity. Porter *et al.* [23] found that a low plasma concentration of GSH-Px constituted a risk factor for coronary disease, and low GSH-Px activity was even detected in atherosclerotic carotid plaques[24]. Patients undergoing haemodialysis were found to have a reduced plasma level of GSH-Px, partially explaining the presence of atherogenesis in chronic kidney disease[25]. Endogenous GSH-Px is an important antioxidant, protecting against oxidative stress in the atherogenic process; a reduction in GSH-Px levels produced by a high intake of fat could contribute to the onset of atherosclerosis associated with postprandial hypertriacylglycerolaemia.

The most relevant finding of the present study, though, is that a high-fat meal that increases oxidative stress produces a decrease in circulating antioxidant defences and in uric acid levels, and that this reduction has a very close association with the increase in oxidative stress.

Uric acid is the final product of purine metabolism in man. In many species, uric acid is metabolized to alantoin by urate oxidase, an enzyme activity that has been lost in man by a defect in gene transcription[26].

In the 1980s, Ames *et al.* proposed that uric acid may have important biological effects as antioxidants, and they showed with *in vitro* experiments that it is a powerful scavenger of reactive oxygen species[27]. Apart from its action as a scavenger of radicals, uric acid also exerts its action chelating metals like iron or copper, converting them into poor reactive species unable to catalyse reactions[28].

Consistent with the antioxidant role of uric acid *in vivo* is the hypothesis that the loss of urate oxidase in man (and the accompanying rise in serum levels of uric acid) improves antioxidant defence. Watanabe *et al.* [29] proposed that high levels of uric acid in man provide an evolutionary advantage as the hyperuricaemia maintains blood pressure better in conditions of low dietary salt intake.

A double-blind study evaluated the effects of the systematic administration of 100 mg uric acid compared with 1000 mg vitamin C[30]. The authors found a significant increase in the antioxidant capacity of the serum after administration of uric acid and vitamin C, but the effect of the uric acid was substantantially greater. Another clinical study suggested an inverse relation between the concentration of uric acid and oxidative

Table 3. Comparisons between experimental conditions before (baseline) and after fat overload†

	Before		After	
	Median	Interquartile range	Median	Interquartile range
TAG (mmol/l)	0·83	0·31	1·60*	0·90
Cholesterol (mmol/l)	5·18	1·45	5·42*	1·38
ApoB (mg/dl)	107	44·75	115	38
NOx (μmol/dl)	158	26·66	169·47	23·58
GSH-Px (U/dl)	6·52	2·02	4·90*	3·20
CAT (U/dl)	9·10	3·27	15·90	3·65
GSH-Rd (U/dl)	25·00	10·88	7·04*	6·86
GST (U/dl)	1·74	1·33	1·88	1·27
SOD (U/dl)	31·79	11·15	41·41	17·32
Uric acid (μmol/l)	288·47	122·52	278·36*	111·22
LPO (mmol/dl)	298	95	407*	150
ProCar (mmol/dl)	10·07	1·61	14·59*	5·12

Median values were significantly different from those of the baseline (Wilcoxon paired-sample test): *$P<0·05$.

†Antioxidant defence variables: CAT, catalase; GSH-Px, glutathione peroxidase; GSH-Rd, glutathione reductase; GST, glutathione-*S*-transferase; SOD, superoxide dismutase. Marker of vasodilatations: NOx, total nitrites (nitrites and nitrates). Pro-oxidant variables: LPO, lipid peroxidation; ProCar, protein carbonyl.

Table 4. Correlations of the differences of the variables studied before and after the overload†

	ΔCAT	ΔUric acid	ΔNOx	ΔSOD	ΔGST	ΔGSH-Rd	ΔProCar	ΔLPO
ΔUric acid	−0·261							
ΔNOx	0·530	0·084						
ΔSOD	0·245	0·020	0·306					
ΔGST	0·145	−0·595*	0·148	−0·279				
ΔGSH-Rd	−0·452	0·211	−0·451	−0·592	0·099			
ΔProCar	−0·490	0·748*	−0·162	−0·035	−0·415	0·294		
ΔLPO	−0·229	−0·436	−0·378	−0·297	−0·192	0·252	−0·093	
ΔTAG post	−0·282	−0·169	−0·201	0·337	−0·383	−0·203	0·291	0·233

TAG post, postprandial TAG; Δ, difference between baseline (before) and after fat overload (increase).
Correlations were significant: *$P<0·05$.
† See Table 3 for abbreviations of variables.

stress during aerobic exercise[31]. High concentrations of circulating uric acid may prevent oxidative stress *in vivo* during intense physical activity and protect against oxidative stress in other situations[32]. The present findings are related with this hypothesis to the extent that we show that uric acid is reduced after acute stress (after a high-fat meal) and that this reduction is supposedly because it exerts its antioxidant effect and is converted into allantoin and other products of oxidation[33]; chronic stress would probably cause an increase in uric acid in order to raise the antioxidant capacity of the plasma. Numerous studies have related uric acid with atherosclerosis[34], but some authors suggest that the development of atherosclerosis is accompanied by a compensatory increase in antioxidant capacity, due mainly to the increased serum levels of uric acid[35]. Experimental findings in animal models found that early elevation of uric acid, during or shortly after acute ischaemic stroke, could confer significant protection against neurological deficit. This is in agreement with the protective effect of uric acid seen in other models of brain disease mediated by free radicals[36].

The close association in the present study between the reduction in uric acid after a high-fat meal and the increase in carbonylated proteins may be explained by the role of uric acid, as it can repair tryptophan indolyl and tyrosine phenoxyl radicals[37], and it is an oxidizable substrate for the haem protein–hydrogen peroxide system, able to protect against oxidative damage, acting as an electron donor[38].

The present findings reinforce the direct association between uric acid and hypertriacylglycerolaemia, where oxidative stress can be the binding factor. We have previously reported the direct relation between TAG levels and uric acid figures[6,7]. The present study, and others, have shown that TAG and postprandial hyperlipidaemia are directly associated with oxidative stress. Uric acid is a powerful antioxidant, and the data from the present study suggest that the reduction seen after a high-fat meal is because it exerts its antioxidant action acutely. The hypothesis may also be completed arguing that the chronic increase in oxidative stress caused by hypertriacylglycerolaemia may produce a chronic increase in uric acid and antioxidant defences which reflects the increase in oxidative stress, thereby raising the antioxidant capacity of the plasma. If this is confirmed, it would reinforce the theory that uric acid is only a marker of risk, and that prudency would be advisable when using uric acid-lowering drugs in patients with hyperuricaemia.

Table 5. Multiple regression analysis (dependent variable: uric acid difference)*

Model 1	β	*T*	*P*
ΔProCar	0·865	4·228	0·006

ΔProCar, protein carbonyl difference between baseline (before) and after fat overload (increase).
* Variables not entering the model: ΔGSH-Rd, ΔCAT, ΔTAG post, ΔGST, ΔLPO, sex and BMI (see Table 3 for abbreviations of variables).

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References

1. Karpe F, Steiner G, Uffelman K, Olivecrona T & Hamsten A (1994) Postprandial lipoproteins and progression of coronary atherosclerosis. *Atherosclerosis* **106**, 83–97.
2. Patsch JR, Miesenbock G, Hopferwieser T, Muhlberger V, Knapp E, Dunn JK, Gotto AM & Patsch W (1992) Relation of triglyceride metabolism and coronary artery disease. *Arterioscler Thromb* **12**, 1336–1345.
3. Cardona F & Tinahones FJ (2006) Relación de la hipertrigliceridemia postprandial con la resistencia a la insulina en pacientes con síndrome metabólico. *Endocrinol Nutr* **53**, 345–352.
4. Bae JH, Bassenge E, Kim KB, Kim YN, Kim KS, Lee HJ, Park KY & Schwemmer M (2001) Postprandial hypertriglyceridemia impairs endothelial function by enhanced oxidant stress. *Atherosclerosis* **155**, 517–523.
5. De Koning EJ & Rabelink TJ (2002) Endothelial function in the postprandial state. *Atheroscler Suppl* **3**, 11–16.
6. Tinahones FJ, Collantes E, C-Soriguer FJ, Gonzalez-Ruiz A, Pineda M, Anon J & Sánchez Guijo P (1995) Increased VLDL

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levels and diminished renal excretion of uric acid in hyperuricaemic–hypertriglyceridaemic patients. *Br J Rheumatol* **34**, 920–924.
7. Tinahones JF, Perez-Lindon G, C-Soriguer FJ, Pareja A, Sanchez-Guijo P & Collantes E (1997) Dietary alterations in plasma very low density lipoprotein levels modify renal excretion of urates in hyperuricemic–hypertriglyceridemic patients. *J Clin Endocrinol Metab* **82**, 1188–1191.
8. Cardona F, Tinahones FJ, Collantes E, Escudero A, Garcia-Fuentes E & Soriguer FJ (2005) Contribution of polymorphisms in the apolipoprotein AI-CIII-AIV cluster to hyperlipidaemia in patients with gout. *Ann Rheum Dis* **64**, 85–88.
9. Cardona F, Tinahones FJ, Collantes E, Escudero A, Garcia-Fuentes E & Soriguer FJ (2003) The elevated prevalence of apolipoprotein E2 in patients with gout is associated with reduced renal excretion of urates. *Rheumatology (Oxford)* **42**, 468–472.
10. Berry CE & Hare JM (2004) Xanthine oxidoreductase and cardiovascular disease: molecular mechanisms and pathophysiological implications. *J Physiol* **16**, 589–606.
11. Maxwell SR, Thomason H, Sandler D, Leguen C, Baxter MA, Thorpe GH, Jones AF & Barnett AH (1997) Antioxidant status in patients with uncomplicated insulin-dependent and non-insulin-dependent diabetes mellitus. *Eur J Clin Invest* **27**, 484–490.
12. Benzie IF, Chung W & Tomlinson B (1999) Simultaneous measurement of allantoin and urate in plasma: analytical evaluation and potential clinical application in oxidant:antioxidant balance studies. *Clin Chem* **45**, 901–904.
13. Lohmann TG, Roche AF & Martorell R (editors) (1988) *Anthropometric Standardization Reference Manual*, Champaign, IL: Human Kinetics Books.
14. Levine RL, Garland D, Oliver CN, Amici A, Climent I, Lenz AG, Ahn BW, Shaltiel S & Stadtman ER (1990) Determination of carbonyl content in oxidatively modified proteins. *Methods Enzymol* **186**, 464–478.
15. Ricart-Jané D, Llobera M & López-Tejero MD (2002) Anticoagulants and other preanalytical factors interfere in plasma nitrate/nitrite quantification by the Griess method. *Nitric Oxide* **6**, 178–185.
16. Flohé L & Gunzler WA (1984) Assays of glutathione peroxidase. *Methods Enzymol* **105**, 114–121.
17. Aebi H (1984) Catalase *in vitro*. *Methods Enzymol* **105**, 121–126.
18. Marklund SL (1990) Analysis of extracellular superoxide dismutase in tissue homogenates and extracellular fluids. *Methods Enzymol* **186**, 260–265.
19. Manuel-y-Keenoy B, Van Campenhout A, Aerts P, Vertommen J, Abrams P, Van Gaal LF, Van Gils C & De Leeuw IH (2005) Time course of oxidative stress status in the postprandial and postabsorptive states in type 1 diabetes mellitus: relationship to glucose and lipid changes. *J Am Coll Nutr* **24**, 474–485.
20. Ursini F & Sevanian A (2002) Postprandial oxidative stress. *Biol Chem* **383**, 599–605.
21. Bowen PE & Borthakur G (2004) Postprandial lipid oxidation and cardiovascular disease risk. *Curr Atheroscler Rep* **6**, 477–484.
22. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, Nakayama O, Makishima M, Matsuda M & Shimomura I (2004) Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest* **114**, 1752–1761.
23. Porter M, Pearson DJ, Suarez-Mendez VJ & Blann AD (1992) Plasma, platelet and erythrocyte glutathione peroxidases as risk factors in ischemic heart disease in man. *Clin Sci* **83**, 343–345.
24. Lapenna D, de Gioia S, Ciofani G, Mezzetti A, Ucchino S, Calafiore AM, Napolitano AM, Di Ilio C & Cuccurullo F (1998) Glutathione-related antioxidant defenses in human atherosclerotic plaques. *Circulation* **97**, 1930–1934.
25. Roxborough HE, Mercer C, McMaster D, Maxwell AP & Young IS (1999) Plasma glutathione peroxidase activity is reduced in hemodialysis patients. *Nephron* **81**, 278–283.
26. Glantzounis GK, Tsimoyiannis EC, Kappas AM & Galaris DA (2005) Uric acid and oxidative stress. *Curr Pharm Des* **11**, 4145–4151.
27. Ames BN, Cathcart R, Schwiers E & Hochstein P (1981) Uric acid provides an antioxidant defense in humans against oxidant- and radical caused aging and cancer: a hypothesis. *Proc Natl Acad Sci U S A* **78**, 6858–6862.
28. Davies KJ, Sevanian A, Muakkassah-Kelly SF & Hochstein P (1986) Uric acid–iron ion complexes. A new aspect of the antioxidant functions of uric acid. *Biochem J* **235**, 747–754.
29. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, Mazzali M & Johnson RJ (2002) Uric acid, hominoid evolution, and the pathogenesis of salt sensitivity. *Hypertension* **40**, 355–360.
30. Waring WS, Webb DJ & Maxwell SR (2001) Systemic uric acid administration increases serum antioxidant capacity in healthy volunteers. *J Cardiovasc Pharmacol* **38**, 365–371.
31. Mikami T, Yoshino Y & Ito A (2000) Does a relationship exist between the urate pool in the body and lipid peroxidation during exercise? *Free Radic Res* **32**, 31–39.
32. Waring WS, Convery A, Mishra V, Shenkin A, Webb DJ & Maxwell SR (2003) Uric acid reduces exercise-induced oxidative stress in healthy adults. *Clin Sci (Lond)* **105**, 425–430.
33. Kaur H & Halliwell B (1990) Action of biologically-relevant oxidizing species upon uric acid. Identification of uric acid oxidation products. *Chem Biol Interact* **73**, 235–247.
34. Franse LV, Pahor M, Di Bari M, Shorr RI, Wan JY, Somes GW & Applegate WB (2000) Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J Hypertens* **18**, 1149–1154.
35. Nieto FJ, Iribarren C, Gross MD, Comstock GW & Cutler RG (2000) Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? *Atherosclerosis* **148**, 131–139.
36. Yu ZF, Bruce-Keller AJ, Goodman Y & Mattson MP (1998) Uric acid protects neurons against excitotoxic and metabolic insults in cell culture, and against focal ischemic brain injury *in vivo*. *J Neurosci Res* **53**, 613–625.
37. Hoey BM & Butler J (1984) The repair of oxidized amino acids by antioxidants. *Biochim Biophys Acta* **791**, 212–218.
38. Halliwell B & Gutteridge JMC (1999) Antioxidant protection by low molecular-mass agents: compounds synthesized in vivo. In *Free Radicals in Biology and Medicine*, pp. 195–197 [B Halliwell and JMC Gutteridge, editors]. Oxford: Oxford University Press.

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