

OXIDANTS, ANTIOXIDANTS, ALCOHOL AND STROKE

Matti Hillbom

University of Oulu, Department of Neurology, Kajaanintie 50, FIN-90220 Oulu Finland

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Antioxidants and stroke
 - 3.1. Cerebrovascular spasms
 - 3.2. Infarct size
 - 3.3. Clinical investigations
4. Alcohol and stroke
 - 4.1. Outcome of stroke
 - 4.2. Occurrence of stroke
5. Atherosclerosis and thrombosis
 - 5.1. Atherogenesis
 - 5.2. Thrombogenesis
6. References

1. ABSTRACT

Free radicals are involved in the formation of both atherosclerosis and thrombosis. Therefore, considerable interest has recently been aroused by their role in the development of ischemic cerebral injury. Experimental observations suggest that antioxidants could reduce cerebral arterial vasospasm, reduce infarct size and prevent the development of both atherosclerosis and thrombosis. However, clinical evidence for these beneficial effects is still lacking.

Alcohol can act as an antioxidant and an oxidant, and its intake seems to exert both beneficial and untoward effects on stroke, depending on drinking habits. Light-to-moderate regular alcohol intake has been suggested to protect against internal carotid artery atherosclerosis, a major cause of ischemic stroke. Ethanol metabolism in human blood vessel walls could antagonize the oxidation of LDL and thereby prevent the development of atherosclerosis. In addition, ethanol and the phenolic compounds of wine could decrease platelet aggregation and thromboxane formation and also prevent thrombus formation. Whether the effects are clinically significant remains to be proved. On the other hand, recent heavy drinking has been observed to worsen vasospastic ischemia caused by subarachnoid bleeding. Whether a lack of antioxidants is responsible for this effect also remains to be proved. Future stroke research should focus on solving these problems.

2. INTRODUCTION

During cerebral ischemia, cytotoxic free radicals are generated. Therefore, agents that impair free radical production may be of potential value in the prevention of cerebral ischemia. Conversely, conditions facilitating the production of free radicals could lead to more severe cerebral ischemia. Alcohol is of interest, because it can act as an oxidant and an antioxidant.

The available epidemiologic evidence suggests that alcohol consumption has both beneficial and untoward effects on the occurrence of stroke. Regular light-to-moderate drinking seems to protect against carotid arterial atherosclerosis, a major risk factor for ischemic stroke (1). On the other hand, recent heavy drinking of alcohol increases the risk for both ischemic and hemorrhagic strokes, but the mediating mechanisms are still unclear (2). The following overview will highlight current evidence of the oxidant/antioxidant actions of alcohol in relation to the risk of stroke.

3. ANTIOXIDANTS AND STROKE

Oxidants seem to play a major role in brain damage caused by cerebrovascular diseases. Several experimental studies have suggested that antioxidants could be of value in both the treatment and the prevention of ischemic stroke. For example, antioxidants may reduce vasospasm and infarct size (3). Another aspect, still poorly investigated, is the role of oxidant/antioxidant status for the incidence and outcome of human strokes.

Strokes are usually divided into the following three categories: *Ischemic brain infarction* (IBI), which is known to have a large number of different causes and/or predisposing factors. Hypertension, cardiac disease and cigarette smoking are the major risk factors of IBI. Spontaneous *intracerebral hemorrhage* (ICH) shares hypertension as a major risk factor with IBI, but also has recent heavy drinking of alcohol and use of anticoagulant treatment as independent risk factors. Finally, aneurysmal *subarachnoid hemorrhage* (SAH) shares cigarette smoking as a major risk factor with IBI. Accordingly, two of the main types of stroke have cigarette smoking as a major risk factor, while the third one has recent heavy drinking of alcohol. Against this background, it is of interest to note that both heavy smokers and heavy drinkers are often short of antioxidant nutrients (4-5).

Oxidants, antioxidants, alcohol and stroke

3.1. Cerebrovascular spasms

Cerebral arterial spasms leading to brain infarction are commonly seen as a complication of aneurysmal SAH. They usually occur about one week after the bleeding and are triggered by blood in the subarachnoid space. In this condition, cerebral vasospasm may result from the action of hemoglobin. According to one hypothesis, free radical formation could be involved. Oxyhemoglobin, which is a potent vasoconstrictor, could trigger a cascade involving phospholipid peroxidation and free radical formation in the vessel wall. Free radicals may impair endothelium dependent vasodilation. The hypothesis is supported by experiments testing the vasospastic action of oxyhemoglobin. Oxyhemoglobin has been observed to produce a slowly developing sustained contraction of canine cerebral arterial rings. Free radical scavenging agents, such as lazaroids and deferoxamine, have been shown to be able to attenuate the effect and the associated elevation of intracellular calcium (6). Perivascular application of deferoxamine has also been shown to inhibit delayed arterial narrowing after chronic blood exposure in a rat femoral artery model of vasospasm (7). These observations suggest that antioxidants could ameliorate experimental vasospasm by scavenging free radicals.

3.2. Infarct size

Another antioxidant, tirilazad mesylate, a 21-aminosteroid lipid-peroxidation inhibitor, has been found to improve early metabolic recovery after severe experimental acidotic cerebral ischemia (8). This observation strongly supports the hypothesis that free radical formation contributes to the appearance of acute cerebral ischemia. Another experimental study showed that tirilazad mesylate is also able to reduce SAH-induced blood-brain barrier damage and to protect cultured neurons against iron-induced lipid peroxidative injury in a concentration-dependent fashion (9). Finally, transgenic mice with a high antioxidant potential in the brain develop smaller experimental infarcts than nontransgenic mice with a lower antioxidant potential (3).

3.3. Clinical investigations

Clinical studies on antioxidants and stroke are rather few in number. One prospective, randomized, double-blind, vehicle-controlled trial on 1,023 patients indicated that tirilazad mesylate can decrease mortality and improve neurological recovery after the onset of aneurysmal subarachnoid hemorrhage (10). In this study the beneficial effect was predominantly seen among men. Part of it may have been due to reduced risk of delayed cerebral ischemia, but this remained unclear, since tirilazad mesylate did not reduce the vasospasm of large cerebral arteries. Vasospasm of large cerebral arteries usually correlate with occurrence of delayed cerebral ischemia. The study was conducted at 41 neurosurgical units in Europe, Australia and New Zealand. One could speculate that tirilazad mesylate was more effective among men, because men were possibly short of antioxidants due to their heavier smoking and drinking compared with women.

The Atherosclerosis Risk in Communities Study (ARIC study) showed a significant inverse relationship

between antioxidant intake (vitamin C and α -tocopherol) and average carotid artery wall thickness both in men and in women (11). The investigators did not adjust for alcohol intake, but adjusted for age, race, education, body mass index, fasting serum glucose, HDL and LDL cholesterol, systolic and diastolic blood pressures, total caloric intake and cigarette smoking. The timing of dietary intake with respect to the development of artery wall thickness was not known. This investigation suggests that an adequate antioxidant supply could prevent the development of carotid arterial atherosclerosis.

The Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study covered 29,133 Finnish male smokers 50 to 69 years of age (12). The follow-up continued for up to 5-8 years. Altogether 110 and 123 deaths due to hemorrhagic and ischemic strokes occurred during the trial. There were more deaths due to ischemic and hemorrhagic strokes among those who received β -carotene than among those who did not. On the other hand, there were fewer deaths caused by ischemic stroke (and ischemic heart disease) among those who received α -tocopherol, but again more deaths due to hemorrhagic stroke.

The Zutphen Study was the first to show a protective effect of flavonoid intake on stroke incidence (13). A cohort of 552 men aged 50 to 69 years was examined in 1970 and followed up for 15 years. Black tea contributed about 70% to flavonoid intake. Men with a high intake of flavonoids had a 73% lower risk of stroke during 15 years of follow-up examinations compared with those with a low intake of flavonoids (adjusted RR 0.31, 95% CI 0.12-0.84). In this study, no association between vitamin C intake and stroke incidence was found, but high β -carotene intake tended to associate with low stroke incidence. Gey and coworkers reported a lower stroke mortality for middle-aged men with high plasma levels of β -carotene (14).

Finally, the Western Electric Study suggested a moderate protective effect of antioxidants on risk of stroke incidence and mortality (15). The analyses were based on 1,843 men, aged 40-55 years at the baseline examination, free of cardiovascular disease, including stroke, through the first follow-up examination in 1959. The highest quartiles of β -carotene, vitamin C intake, and antioxidant index were associated with decreased risk of stroke by 16, 29 and 26%, respectively, compared to the lowest quartile. Further large trials are needed before the question of whether antioxidants will reduce the incidence of stroke can be answered.

4. ALCOHOL AND STROKE

4.1. Outcome of stroke

The outcome of stroke seems to be influenced by recent heavy drinking of alcohol. After adjustment for several other risk factors, recent heavy drinking remained a significant independent predictor of poor outcome in both patients with aneurysmal SAH and ones with spontaneous ICH (16-17). However, infrequent drinking seems to be harmless with respect to the outcome. One could speculate

Oxidants, antioxidants, alcohol and stroke

that the antioxidant status of the patients influenced the outcome. A shortage of antioxidants among recent heavy drinkers could have caused more severe vasospasms and larger brain infarctions after the bleeding. The hypothesis was supported by the finding that the poor outcome of the heavily drinking SAH patients was frequently caused by cerebral vasospastic ischemia, although rebleedings and larger bleedings were also found to be responsible for the poor outcome (16-17).

Antioxidant deficiencies are common both among recent heavy drinkers (5) and among regular heavy smokers (4). Interestingly, heavy drinking of alcohol remained a significant predictor of poor outcome even after adjustment for cigarette smoking (16). Therefore, other alcohol-related factors could also have contributed to the poor outcome. For example, the alcohol withdrawal syndrome, which frequently follows an abrupt cessation of prolonged heavy drinking, is associated with wellknown cerebral disorders that could influence the outcome of stroke. By using unilateral carotid artery ligation in gerbils, it has been shown that experimental ischemic cerebral infarcts are larger if they are precipitated at the onset of alcohol withdrawal (18).

4.2. Occurrence of stroke

The occurrence of stroke could also be influenced by antioxidant deficiencies. The high morbidity and mortality from stroke among 15 European Communist populations has been speculated to be related to antioxidant deficiencies (19). It is wellknown that the consumption of alcohol is high and that of fruit low among these people.

According to a recent report, lacunar cerebral infarction is common among young adults who are alcohol misusers (20). Lacunar stroke originates from the small penetrating arteries of deep cerebral structures. Hypertension is the major risk factor for both lacunar hemorrhage and infarction. Diabetes and cigarette smoking are also risk factors for lacunar infarction. The role of alcohol drinking as a risk factor for lacunar stroke has not been thoroughly investigated.

The exact mechanism leading to lacunar stroke is unclear. However, hypertension promotes degeneration of the small penetrating arteries leading to microaneurysm formation. Interestingly, the wellknown antiatherogenic effect of alcohol intake may not be operating in the small penetrating cerebral arteries (21), and alcohol has not been found to increase prostacyclin formation in rat brain microvessels (22). Accordingly, the actions of alcohol could be different, depending on vessel type. The effects of alcohol on the small cerebral arteries compared to the other arteries in humans need to be investigated, because several studies have demonstrated alcohol-induced vasospasms in the cerebral arteries of experimental animals (23-24). In addition, pretreatment of rats with α -tocopherol has been shown to ameliorate the cerebrovasospasm and vascular damage induced by alcohol (25). Before we can answer the question of whether alcohol-induced vasoconstriction is involved in the precipitation of lacunar strokes, we need to demonstrate that lacunar strokes frequently occur during

severe alcoholic intoxication, and that recent heavy drinking is an independent risk factor for lacunar stroke. Alcohol-induced hypertension could also mediate the risk.

How about the oxidative status? A recent experimental study explored the effects of alcohol on nitric oxide mediated cerebral arteriolar dilation. According to the results, it is possible that alcohol-stimulated release of oxygen radicals could impair cerebral vasodilation by a direct effect of oxygen radicals on nitric oxide. However, the effect was not demonstrated by low and moderate alcohol concentrations (26). I would like to conclude that the role of alcohol as well as that of the oxidative status in the pathogenesis of lacunar stroke is still highly speculative. However, the abovementioned aspects should also be investigated in normotensive and hypertensive human subjects.

5. ATHEROSCLEROSIS AND THROMBOSIS

Much attention has recently been paid to the possible beneficial effect of moderate alcohol consumption on both athero- and thrombogenesis. The antioxidant effects of ethanol itself and some other components of alcoholic beverages can be considered to inhibit these processes.

5.1. Atherogenesis

First, ethanol can act as an antioxidant and inhibit low density lipoprotein (LDL) oxidation. Because the oxidation of LDL promotes the development of atherosclerosis in vivo (27), it has been hypothesized that ethanol metabolism, if it occurs in human blood vessel walls to a significant extent, could protect against the development of atherosclerosis by antagonizing the oxidation of LDL (28). However, the available clinical evidence does not consistently support the hypothesis (1-2, 29-31). Although both coronary and carotid atherosclerosis have frequently been reported to be less common among regular light-to-moderate drinkers than life-long abstainers, mortality from coronary heart disease is high among both regular heavy drinkers and life-long abstainers (30-31). One could anticipate that the higher the dose of alcohol, the lesser of the risk for atherosclerosis and coronary heart disease, but this is not the case. Confounding factors, such as cigarette smoking and hypertension, could explain the discrepancy, but they seem to be eliminated (30-31). Apparently, other effects caused by prolonged heavy drinking, among them antioxidant deficiency, should be taken into account. In fact, some experimental data indicate that a high dose of alcohol raises LDL (32) and a high level of LDL stimulates platelet thromboxane formation (33).

Second, LDL oxidation could be inhibited by some antioxidant compounds of alcoholic beverages, such as tannins. Particularly red wine, but also white wine, contain these phenolic substances, which are powerful antioxidants, and it has been shown that the phenolic compounds of red wine inhibit the oxidation of human LDL (34).

5.2. Thrombogenesis

Third, the antioxidants of wine also inhibit platelet aggregation, and the inhibitory effect seems to

Oxidants, antioxidants, alcohol and stroke

prevail for some time even after the cessation of drinking (35). This could explain the findings that light-to-moderate drinking, but not heavy drinking, prevents coronary heart disease and ischemic stroke, because in most countries heavy drinkers use alcoholic beverages other than wine. The most recent *in vitro* studies have demonstrated that even dealcoholized red wines clearly inhibit platelet aggregation (36). This provides evidence to support the hypothesis that the antioxidants of wine, at least in part, are responsible for the effect. This is also in line with the observation that coronary heart disease mortality is low in wine-drinking countries.

Many previous *in vitro* experiments suggest that ethanol itself can inhibit platelet reactivity (37). However, the effect is short-lasting. Concerning acute alcohol intake by human nonalcoholic volunteers, conflicting observations have been reported. Acute alcohol intake has been observed to decrease and increase platelet reactivity. A rebound increase after an initial decrease in platelet aggregation may occur (38).

Farmers from France, who are wine drinkers, show an inverse association between preceding alcohol intake and platelet reactivity, e.g. the more alcohol they have consumed, the less platelet reactivity they show (39). We do not know whether this finding is due to the effects of ethanol itself or those of some other components of wine, but people from Great Britain also show a similar association (40). In order to test this, we recently gave a moderate amount of red wine to healthy human Finnish volunteers who were light occasional drinkers. We observed that a moderate dose of red wine, when taken together with an evening meal or after fasting for 6 hours, caused a significant decrease in shear-induced platelet aggregation, which prevailed for the time the alcohol was present in blood, i.e. for 8 hours (Numminen *et al.*, unpublished observation). Unfortunately, we did not use a control group ingesting pure ethanol, but the addition of a large amount of ethanol to a test tube increased platelet reactivity, whereas an addition of red wine did not.

6. REFERENCES

1. Camargo CA Jr.: Case-control and cohort studies of moderate alcohol consumption and stroke. *Clin Chim Acta* 246:107-119 (1996)
2. Hillbom M: Neurological damage - stroke. In: Effects of Ethanol on the Central Nervous System. Eds: Dietrich RA, Erwin VG, CRC Press, New York, pp 383-408 (1996)
3. Chan PH: Role of oxidants in ischemic brain damage. *Stroke* 27:1124-1129 (1996)
4. Margetts BM & AA Jackson: Interactions between people's diet and their smoking habits: the dietary and nutritional survey of British adults. *Br Med J* 307:1381-1384 (1993)
5. Ward RJ & TJ Peters: The antioxidant status of patients with either alcohol-induced liver damage or myopathy. *Alcohol* 27:359-365 (1992)
6. Vollrath B, P Chan, M Findlay & D Cook: Lazaroids and deferoxamine attenuate the intracellular effects of oxyhaemoglobin in vascular smooth muscle. *Cardiovasc Res* 30:619-626 (1995)
7. Luo Z, T Harada, S London, C Gajdusek & MR Mayberg: Antioxidant and iron-chelating agents in cerebral vasospasm. *Neurosurgery* 37:1154-1158 (1995)
8. Kim H, RC Koehler, PD Hurn, ED Hall & RJ Traystman: Amelioration of impaired cerebral metabolism after severe acidotic ischemia by tirilazad posttreatment in dogs. *Stroke* 27:114-121 (1996)
9. Smith SL, HM Scherch & ED Hall: Protective effects of tirilazad mesylate and metabolite U-89678 against blood-brain barrier damage after subarachnoid hemorrhage and lipid peroxidative neuronal injury. *J Neurosurg* 84:229-233 (1996)
10. Kassell NF, EC Haley Jr, C Apperson-Hansen & WM Alves: Randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in Europe, Australia, and New Zealand. *J Neurosurg* 84:221-228 (1996)
11. Kritchevsky SB, T Shimakawa, GS Tell, B Dennis, M Carpenter, JH Eckfeldt, H Peacher-Ryan & G Heiss: Dietary antioxidants and carotid artery wall thickness. The ARIC Study. Atherosclerosis Risk in Communities Study. *Circulation* 92:2142-2150 (1995)
12. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group: The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 330:1029-1035 (1994)
13. Keli SO, MGL Hertog, EJM Feskens & D Kromhout: Dietary flavonoids, antioxidant vitamins, and incidence of stroke. *Arch Intern Med* 154:637-642 (1996)
14. Gey KF, HB Stahelin & M Eichholzer: Poor plasma status of carotene and vitamin C is associated with higher mortality from ischemic heart disease and stroke: prospective Basel Study. *Clin Invest* 71:3-6 (1993)
15. Daviglus ML, AJ Orenca, AR Dyer, K Liu, DK Morris, V Persky, N Chavez, J Goldberg, M Drum, RB Shekelle & J Stamler: Dietary vitamin C, beta-carotene and 30-year risk of stroke: results from the Western Electric Study. *Neuroepidemiology* 16:69-77 (1997)
16. Juvela S: Alcohol consumption as a risk factor for poor outcome after aneurysmal subarachnoid haemorrhage. *Br Med J* 304:1663-1667 (1992)
17. Juvela S: Risk factors for impaired outcome after spontaneous intracerebral hemorrhage. *Arch Neurol* 52:1193-1200 (1995)
18. Mandybur TI & CL Mendenhall: The effects of chronic alcoholism on development of ischemic cerebral

Oxidants, antioxidants, alcohol and stroke

infarcts following unilateral carotid artery ligation in gerbils. *Alcoholism Clin Exp Res* 7:357-361 (1983)

19. Ginter E: Cardiovascular risk factors in the former communist countries. Analysis of 40 European MONICA populations. *Eur J Epidemiol* 11:199-205 (1995)

20. Qureshi AI, K Safdar, M Patel, RS Janssen & MR Frankel: Stroke in young black patients. Risk factors, subtypes, and prognosis. *Stroke* 26:1995-1998 (1995)

21. Reed DM, JA Resch, T Hayashi, C MacLean & KA Yano: A prospective study of cerebral artery arteriosclerosis. *Stroke* 19:820-825 (1988)

22. Pediconi M, C Colombo & C Galli: Ethanol administration in the rat decreases prostacyclin production by isolated brain microvessels. *J Neurochem* 46:1458-1463 (1986)

23. Altura BM, BT Altura & A Gebrewold: Alcohol-induced spasms of cerebral blood vessels: Relation to cerebrovascular accidents and sudden death. *Science* 220:331-333 (1983)

24. Gordon EL, T-S Nguyen, AC Ngai & HR Winn: Differential effects of alcohols on intracerebral arterioles. Ethanol alone causes vasoconstriction. *J Cereb Blood Flow Metab* 15:532-538 (1995)

25. Altura BM & A Gebrewold: a-Tocopherol attenuates alcohol-induced cerebral vascular damage in rats: possible role of oxidants in alcohol brain pathology and stroke. *Neurosci Lett* 220:207-210 (1996)

26. Mayhan WG & SP Didion: Acute effects of ethanol on responses of cerebral arterioles. *Stroke* 26:2097-2102 (1995)

27. Ylä-Herttua S, W Palinski, ME Rosenfeld, S Parthasarathy, TE Carew, S Butler, JL Witztum & D Steinberg: Evidence for the presence of oxidatively modified low density lipoprotein in atherosclerotic lesions of rabbit and man. *J Clin Invest* 84:1086-1095 (1989)

28. Bello AT, NS Bora, LG Lange & PS Bora: Cardioprotective effects of alcohol: Mediation by human vascular alcohol dehydrogenase. *Biochem Biophys Res Commun* 203:1858-1864 (1994)

29. Rissanen V: Coronary and aortic atherosclerosis in chronic alcoholics. *Z Rechtsmed* 75:183-189 (1974)

30. Paunio M, J Virtamo, C-G Gref & OP Heinonen: Serum high density lipoprotein cholesterol, alcohol, and coronary mortality in male smokers. *Br Med J* 312:1200-1203 (1996)

31. Wannamethee SG & G Shaper: Patterns of alcohol intake and risk of stroke in middle-aged British men. *Stroke* 27:1033-1039 (1996)

32. Hojnacki JL, JE Cluette-Brown, RN Dechenes, JJ Mulligan, TV Osmolski, NJ Rencricca & JJ Barboriak: Alcohol produces dose-dependent antiatherogenic and

atherogenic plasma lipoprotein responses. *Proc Soc Exp Biol Med* 200:67-77 (1992)

33. Beitz J, H-U Block, A Beitz, G Muller, L Winkler, R Dargel & H-J Mest: Endogenous lipoproteins modify the thromboxane formation capacity of platelets. *Atherosclerosis* 60:95-99 (1986)

34. Frankel EN, J Kanner, JB German, E Parks & JE Kinsella: Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. *Lancet* 341:454-457 (1993)

35. Ruf J-C, J-L Berger & S Renaud: Platelet rebound effect of alcohol withdrawal and wine drinking in rats. Relation to tannins and lipid peroxidation. *Arterioscler Thromb Vasc Biol* 15:140-144 (1995)

36. Pace-Asciak CR, S Hahn, EP Diamandis, G Soleas & DM Goldberg: The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease. *Clin Chem Acta* 235:207-219 (1995)

37. Rubin R & ML Rand: Alcohol and platelet function. *Alcohol Clin Exp Res* 18:105-110 (1994)

38. Renaud SC & J-C Ruf: Effects of alcohol on platelet functions. *Clin Chim Acta* 246:77-89 (1996)

39. Renaud S, E Dumont, F Godsey, A Supplisson & C Thevenon: Platelet functions in relation to dietary fats in farmers from two regions of France. *Thromb Haemost* 40:518-531 (1979)

40. Meade TW, MV Vickers, SG Thompson, Y Stirling, AP Haine & GJ Miller: Epidemiological characteristics of platelet aggregability. *Br Med J* 290:428-432 (1985)

Key words: Alcohol Oxidants Antioxidants Stroke, Review

Send correspondence to: Professor Matti Hillbom, MD, University of Oulu, Department of Neurology, Kajaanintie 50, FIN-90220 Oulu, Finland, Europe, Tel. +358 8 315 4518, Fax. +358 8 315 4544, E-mail: matti.hillbom@oulu.fi

Received: 5/1/99 Accepted: 5/20/99