














ARRHYTHMIA (CARDIAC)

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of action

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Journal of Nutrition (USA), 1997, 127/3 (383-393)

The role of marine fish oil (n-3) polyunsaturated fatty acids in the prevention of fatal ventricular arrhythmia has been established in experimental animals. Prevention of arrhythmias arising at the onset of ischemia and reperfusion is important because if untreated, they result in sudden cardiac death. Animals supplemented with fish oils in their diet developed little or no ventricular fibrillation after ischemia was induced. Similar effects have also been observed in cultured neonatal cardiomyocytes. Several mechanisms have been proposed and studied to explain the antiarrhythmic effects of fish oil polyunsaturated fatty acids, but to date, no definite mechanism has been validated. The sequence of action of these mechanisms and whether more than one mechanism is involved is also not clear. Some of the mechanisms suggested to explain the antiarrhythmic action of fish oils include the incorporation and modification of cell membrane structure by (n-3) polyunsaturated fatty acids, their direct effect on calcium channels and cardiomyocytes and their role in eicosanoid metabolism. Other mechanisms that are currently being investigated include the role of (n-3) polyunsaturated fatty acids in cell signalling mediated through phosphoinositides and their effect on various enzymes and receptors. This article reviews these mechanisms and the antiarrhythmic studies using (n-3) polyunsaturated fatty acids.

Fatty acids suppress voltage-gated Na⁺ currents in HEK293t cells transfected with the alpha-subunit of the human cardiac Na⁺ channel

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Proceedings of the National Academy of Sciences of the United States of America (United States), 1998, 95/5 (2680-2685)

Studies have shown that fish oils, containing n-3 fatty acids, have protective effects against ischemia-induced, fatal cardiac arrhythmias in animals and perhaps in humans. In this study we used the whole-cell voltage-clamp technique to assess the effects of dietary, free long-chain fatty acids on the Na⁺ current (I(Na,α)) in human embryonic kidney (HEK293t) cells transfected with the alpha-subunit of the human cardiac Na⁺ channel (hH1(α)). Extracellular application of 0.01 to 30 μM eicosapentaenoic acid (EPA, C20:5n-3) significantly reduced I(Na,α) with an IC₅₀ of 0.51 plus or minus 0.06 μM. The EPA-induced suppression of I(Na,α) was concentration- and voltage- dependent. EPA at 5 μM significantly shifted the steady-state inactivation relationship by -27.8 plus or minus 1.2 mV (n = 6, P < 0.0001) at the V_{1/2} point. In addition, EPA blocked I(Na,α) with a higher 'binding affinity' to hH1(α) channels in the inactivated state than in the resting state. The transition from the resting state to the inactivated state was markedly accelerated in the presence of 5 μM EPA. The time for 50% recovery from the inactivation state was significantly slower in the presence of 5 μM EPA, from 2.1 plus or minus 0.8 ms for control to 34.8 plus or minus 2.1 ms (n = 5, P < 0.001). The effects of EPA on I(Na,α) were reversible. Furthermore, docosahexaenoic acid (C22:6n-3), alpha-linolenic acid (C18:3n-3), conjugated linoleic acid (C18:2n-7), and oleic acid (C18:1n-9) at 5 μM and all-trans-retinoic acid at 10 μM had similar effects on I(Na,α) as EPA. Even 5 μM of stearic acid (C18:0) or palmitic acid (C16:0) also significantly inhibited I(Na,α). In contrast, 5 μM EPA ethyl ester did not alter I(Na,α) (8 plus or minus 4%, n = 8, P > 0.05). The present data demonstrate that free fatty acids suppress I(Na,α) with high 'binding affinity' to hH1(α) channels in the inactivated state and prolong the duration of recovery from inactivation.

n-3 Polyunsaturated fatty acids, heart rate variability and ventricular arrhythmias in patients with previous myocardial infarcts

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Ugeskrift for Laeger (Denmark), 1997, 159/37 (5525-5529)

There is evidence for an antiarrhythmic effect of n-3 polyunsaturated fatty acids (n-3 PUFA) in animals. The aim of the present study was to investigate the effect of dietary n-3 PUFA on ventricular arrhythmias and heart rate variability (HRV) in patients with a previous myocardial infarction. Fifty-five patients were randomized to receive either 5.2 g of n-3 PUFA daily for 12 weeks or placebo in a double blind, placebo-controlled study. Prior to randomization a 24-hour Holter recording was obtained, and this was repeated at the end of the study. The major end-points were the number of ventricular extrasystoles (VE)/24 hours and the 24-hour HRV. A non-significant decrease in VE/24 hours was found in both the n-3 PUFA group and among controls after dietary supplementation, whereas HRV significantly increased after n-3 PUFA compared to both baseline values (p = 0,04) and to controls (p = 0,01). The present study therefore supports the hypothesis that n-3 PUFA may have an antiarrhythmic effect in humans.

Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: The Indian experiment of infarct survival - 4

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Cardiovascular Drugs and Therapy (USA), 1997, 11/3 (485-491)

In a randomized, placebo-controlled trial, the effects of treatment with fish oil (eicosapentaenoic acid, 1.08 g/day) and mustard oil (alpha-linolenic acid, 2.9 g/day) were compared for 1 year in the management of 122 patients (fish oil, group A), 120 patients (mustard oil, group B), and 118 patients (placebo, group C) with suspected acute myocardial infarction (AMI). Treatments were administered about (mean) 18 hours after the symptoms of AMI in all three groups. The extent of cardiac disease, rise in cardiac enzymes, and lipid peroxides were comparable among the groups at entry into the study. After 1 year total cardiac events were significantly less in the fish oil and mustard oil groups compared with the placebo group (24.5% and 28% vs. 34.7%, $p < 0.01$). Nonfatal infarctions were also significantly less in the fish oil and mustard oil groups compared with the placebo group (13.0% and 15.0% vs. 25.4%, $p < 0.05$). Total cardiac deaths showed no significant reduction in the mustard oil group; however, the fish oil group had significantly less cardiac deaths compared with the placebo group (11.4% vs. 22.0%, $p < 0.05$). Apart from the decrease in the cardiac event rate, the fish oil and mustard oil groups also showed a significant reduction in total cardiac arrhythmias, left ventricular enlargement, and angina pectoris compared with the placebo group. Reductions in blood lipoproteins in the two intervention groups were modest and do not appear to be the cause of the benefit in the two groups. Diene conjugates showed a significant reduction in the fish oil and mustard oil groups, indicating that a part of the benefit may be caused by the reduction in oxidative stress. The findings of this study suggest that fish oil and mustard oil, possibly due to the presence of n-3 fatty acids, may provide rapid protective effects in patients with AMI. However, a large study is necessary to confirm this suggestion.

omega3 fatty acids in the prevention-management of cardiovascular disease

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Canadian Journal of Physiology and Pharmacology (Canada), 1997, 75/3 (234-239)

Epidemiologic studies show that populations who eat fish versus those who do not have a reduced death rate from cardiovascular disease. Experimental studies have shown that omega-3 fatty acids affect the function of cells involved in atherothrombosis in numerous ways, including the modification of eicosanoid products in the cyclooxygenase and lipoxygenase pathways, the reduced synthesis of cytokines and platelet-derived growth factor, and alterations of leukocyte and endothelial cell properties. Intervention studies in patients with restenosis, myocardial infarction, and cardiac arrhythmias with omega-3 fatty acid supplementation have been addressed in several clinical studies. The ingestion of omega-3 fatty acids following one episode of myocardial infarction appears to decrease the rate of cardiac death. These effects of omega-3 fatty acids appear to be due to their antiarrhythmic properties. In fact, fish oil has been shown to reduce ventricular arrhythmias and to be more beneficial than currently used pharmacologic agents. The dose, duration, and mechanisms involved in the prevention and management of cardiovascular disease following omega-3 fatty acid ingestion or supplementation need to be investigated by double blind controlled clinical trials.

Omega-3 fatty acids and prevention of cardiovascular disease

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Cahiers de Nutrition et de Dietetique (France), 1997, 32/2 (107-114)

Most of the cardio-vascular disease (CVD) risk factors may be controlled by nutrition. Polyunsaturated fatty acids (PUFA) of the omega3 series are known for their beneficial effect on risk, but could also influence the CVD severity through their action on the heart, very sensitive to diet-induced alterations of membrane composition. Introducing omega3 PUFA in the diet results in an inversion of the AA/DHA ratio, mainly due to an increase in DHA content. In several experimental models, such structural changes were reported to affect cardiac functions. Arrhythmia which occurs during ischemia and reperfusion, is largely reduced when the membrane contains 20% DHA. Moreover, the membrane omega3 PUFA appear to increase energy utilization efficiency. This may be related to the positive effect of fish oil on the decrease of heart rate in rat in vivo, and on the recovery of mitochondrial function in

the post-ischemic heart. At a more cellular level, the omega3 PUFAs (particularly DHA) can influence the activity of phospholipase A2, which contributes to membrane homeostasis, the prostaglandin production or the function of adrenergic receptors, a key system in the regulation of cardiac activity. Quite similar effects were reported in pathological conditions since the presence of omega3 PUFAs in the membranes enhances the cellular recovery after hypoxia and blocks the stimulation of prostacycline synthesis induced by post-hypoxic reoxygenation. However, much research remains to be done, in order to understand the interactions between diet-induced membrane alterations and cardiac physiology, pathology, and pharmacology.

Vitamin E analogues reduce the incidence of ventricular fibrillations and scavenge free radicals

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Fundamental and Clinical Pharmacology (France), 1998, 12/2 (164-172)

The aim of our study was to analyse the protective effects of different alpha-tocopherol analogues 1) against fibrillations induced by an ischemia-reperfusion sequence, and 2) to further investigate in vitro the radical scavenging properties of these analogues by two sensitive methods. Concerning 1: isolated rat hearts underwent 10 min of coronary ligation followed by reperfusion and the alpha-tocopherol analogues were infused 15 min before occlusion. Functional parameters including heart rate and fibrillations were recorded. Concerning 2: the beta-phycoerythrin assay was utilised to determine the oxygen radical absorbing capacity: (ORAC) of these vitamin E analogues against peroxy radicals. Electron paramagnetic resonance (EPR) was used to measure their scavenger abilities on hydroxyl radical and superoxide anion production. Concerning 1: ventricular fibrillation times were reduced for all analogues treated hearts at concentrations of 1 microM and 5 microM, with Trolox being the most efficacious. Concerning 2: in our experimental conditions of intense production of free radicals, scavenging IC50 values for hydroxyl radical were 1.15, 2.17 and 4.04 mM for Trolox, MDL 74270 and MDL 74366 respectively. Superoxide anion IC50 values were 1.0 and 6.75 mM for Trolox and MDL 74270. Our results show that water-soluble analogues of vitamin E are effective in the prevention of coronary ligation induced reperfusion arrhythmia under our experimental conditions. Moreover, our data demonstrate that these vitamin E analogues are effective scavengers for a variety of radicals. Our studies support the view that compounds that can either inhibit the formation or scavenge free radicals can protect the heart against arrhythmia associated with ischemia-reperfusion.

Antioxidant activity of U-83836E, a second generation lazaroid, during myocardial Ischemia/Reperfusion injury

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Free Radical Research (United Kingdom), 1997, 27/6 (577-590)

The 21-aminosteroid compounds are potent lipid per oxidation inhibitors belonging to a new class of antioxidants given the collective name of 'lazaroids'. They protect cells from oxidative damage induced by oxygen-based free radicals in a variety of in vitro and in vivo test systems. U-83836E is one of the second-generation lazaroids that are based on a non steroidal structure characterized by a ring portion of alpha-tocopherol bonded with various amine groups. We investigated the ability of U-83836E to reduce myocardial damage in rats undergoing left coronary artery occlusion for 60 min followed by 6 hours of reperfusion. This ischemia/reperfusion model produced wide heart necrosis, membrane lipid peroxidation, ventricular arrhythmias, tissue neutrophil infiltration and a marked decrease in endogenous antioxidants. Intravenous administration of U-83836E, (7.5, 15 and 30 mg/kg) at onset of reperfusion, reduced myocardial necrosis, expressed as a percentage of either the area at risk or the total left ventricle ($p < 0.001$), improved haemodynamic conditions by decreasing ventricular arrhythmias ($p < 0.005$), limited membrane lipid peroxidation (evaluated by assessing conjugated dienes, $p < 0.001$; and 4-hydroxy-nonenal, $p < 0.001$) restored the endogenous antioxidants vitamin E ($p < 0.001$), and superoxide dismutase ($p < 0.001$). Furthermore, the lazaroid inhibited the derimental hydroxyl radical formation ($p < 0.001$), evaluated indirectly by a trapping agent and reduced heart neutrophil infiltration, measured by testing cardiac tissue elastase ($p < 0.001$) that is released from the stimulated granulocytes at the site of injury. These data suggest that this compound could be a new useful tool to study the mechanisms of oxidative damage during myocardial infarction.

Trace elements and cardioprotection: Increasing endogenous glutathione peroxidase activity by oral selenium supplementation in rats limits reperfusion-induced arrhythmias

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Oxyradicals have been implicated as a possible cause of reperfusion- arrhythmias (RA). However, the use of diverse exogenous oxyradical scavengers designed to reduce RA has given contradictory results. The aim of the present study was to determine whether enhancing the activity of the main endogenous enzyme involved in peroxide elimination in cardiac cells, namely glutathione peroxidase, may limit RA in isolated heart preparations by increasing their antioxidant status. For this purpose, a group of 15 male Wistar rats received a selenium enriched diet for ten weeks (1.5 mg Se/kg diet). Control animals (n=15) received a standard diet containing 0.05 mg Se/kg diet. The incidence of early ventricular arrhythmias was investigated during the reperfusion period following 10 min regional ischemia induced ex-vivo by left coronary artery ligation. Our results show that selenium-supplementation significantly increased the global selenium status of the animals. In the isolated heart preparations, the selenium supplementation induced a significant reduction of the severity of RA as assessed by the arrhythmia score and the limitation of the incidence of both ventricular tachycardia (control: 91% vs, selenium: 36%, $p < 0.05$) and irreversible ventricular fibrillation (control: 45% vs selenium: 0%, $p < 0.05$). These effects were associated with a significant increase in cardiac mitochondrial and cytosolic glutathione peroxidase activities in both the left and the right ventricles. These results illustrate the potential protective effect of selenium against ischemia- reperfusion injury and suggest that peroxides might play a key role in the genesis of some aspects of the reperfusion syndrome.

Randomized, double-blind placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction

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Cardiovascular Drugs and Therapy (United States), 1998, 12/4 (347-353)

The effects of oral treatment with coenzyme Q10 (120 mg/d) were compared for 28 days in 73 (intervention group A) and 71 (placebo group B) patients with acute myocardial infarction (AMI). After treatment, angina pectoris (9.5 vs. 28.1), total arrhythmias (9.5% vs. 25.3%), and poor left ventricular function (8.2% vs. 22.5%) were significantly ($P < 0.05$) reduced in the coenzyme and group than placebo group. Total cardiac events, including cardiac deaths and nonfatal infarction, were also significantly reduced in the coenzyme Q10 group compared with the placebo group (15.0% vs. 30.9%, $P < 0.02$). The extent of cardiac disease, elevation in cardiac enzymes, and oxidative stress at entry to the study were comparable between the two groups. Lipid peroxides, diene conjugates, and malondialdehyde, which are indicators of oxidative stress, showed a greater reduction in the treatment group than in the placebo group. The antioxidants vitamin A, E, and C and beta-carotene, which were lower initially after AMI, increased more in the coenzyme Q10 group than in the placebo group. These findings suggest that coenzyme Q10 can provide rapid protective effects in patients with AMI if administered within 3 days of the onset of symptoms. More studies in a larger number of patients and long-term follow-up are needed to confirm our results.

Effect of coenzyme Q10 therapy in patients with congestive heart failure: A long-term multicenter randomized study

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Clin. Invest. Suppl. (Germany), 1993, 71/8 (S 134-S 136)

The improved cardiac function in patients with congestive heart failure treated with coenzyme Q10 supports the hypothesis that this condition is characterized by mitochondrial dysfunction and energy starvation, so that it may be ameliorated by coenzyme Q10 supplementation. However, the main clinical problems in patients with congestive heart failure are the frequent need of hospitalization and the high incidence of life-threatening arrhythmias, pulmonary edema, and other serious complications. Thus, we studied the influence of coenzyme Q10 long-term treatment on these events in patients with chronic congestive heart failure (New York Heart Association functional class III and IV) receiving conventional treatment for heart failure. They were randomly assigned to receive either placebo (n = 322, mean age 67 years, range 30-88 years) or coenzyme Q10 (n = 319, mean age 67 years, range 26-89 years) at the dosage of 2 mg/kg per day in a 1-year double-blind trial. The number of patients who required hospitalization for worsening heart failure was smaller in the coenzyme Q10 treated group (n = 73) than in the control group (n = 118, $P < 0.001$). Similarly, the episodes of pulmonary edema or cardiac asthma were reduced in the control group (20 versus 51 and 97 versus 198, respectively; both $P < 0.001$) as compared to the placebo group. Our results demonstrate that the addition of coenzyme Q10 to conventional therapy significantly reduces hospitalization for worsening of heart failure and the incidence of serious complications

in patients with chronic congestive heart failure.

Serum concentration of lipoprotein(a) decreases on treatment with hydrosoluble coenzyme Q10 in patients with coronary artery disease: discovery of a new role.

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Int J Cardiol 1999 Jan;68(1):23-9

OBJECTIVE: To examine the effect of coenzyme Q10 supplementation on serum lipoprotein(a) in patients with acute coronary disease.

STUDY DESIGN: Randomized double blind placebo controlled trial.

SUBJECTS AND METHODS: Subjects with clinical diagnosis of acute myocardial infarction, unstable angina, angina pectoris (based on WHO criteria) with moderately raised lipoprotein(a) were randomized to either coenzyme Q10 as Q-Gel (60 mg twice daily) (coenzyme Q10 group, n=25) or placebo (placebo group, n=22) for a period of 28 days.

RESULTS: Serum lipoprotein(a) showed significant reduction in the coenzyme Q10 group compared with the placebo group (31.0% vs 8.2% $P < 0.001$) with a net reduction of 22.6% attributed to coenzyme Q10. HDL cholesterol showed a significant increase in the intervention group without affecting total cholesterol, LDL cholesterol, and blood glucose showed a significant reduction in the coenzyme Q10 group. Coenzyme Q10 supplementation was also associated with significant reductions in thiobarbituric acid reactive substances, malonaldehyde and diene conjugates, indicating an overall decrease in oxidative stress.

CONCLUSION: Supplementation with hydrosoluble coenzyme Q10 (Q-Gel) decreases lipoprotein(a) concentration in patients with acute coronary disease.

Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects.

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Proc Natl Acad Sci U S A 1998 Jul 21;95(15):8892-7

Coenzyme Q10 is an essential cofactor of the electron transport chain as well as a potent free radical scavenger in lipid and mitochondrial membranes. Feeding with coenzyme Q10 increased cerebral cortex concentrations in 12- and 24-month-old rats. In 12-month-old rats administration of coenzyme Q10 resulted in significant increases in cerebral cortex mitochondrial concentrations of coenzyme Q10. Oral administration of coenzyme Q10 markedly attenuated striatal lesions produced by systemic administration of 3-nitropropionic acid and significantly increased life span in a transgenic mouse model of familial amyotrophic lateral sclerosis. These results show that oral administration of coenzyme Q10 increases both brain and brain mitochondrial concentrations. They provide further evidence that coenzyme Q10 can exert neuroprotective effects that might be useful in the treatment of neurodegenerative diseases.

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Magnesium in supraventricular and ventricular arrhythmias

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Zeitschrift für Kardiologie (Germany), 1996, 85/Suppl. 6 (135-145)

The use of magnesium as an antiarrhythmic agent in ventricular and supraventricular arrhythmias is a matter of an increasing but still controversial discussion during recent years. With regard to the well established importance of magnesium in experimental studies for preserving electrical stability and function of myocardial cells and tissue, the use of magnesium for treating one or the other arrhythmia seems to be a valid concept. In addition, magnesium application represents a physiologic approach, and by this, is simple, cost-effective and safe for the patient. However, when one reviews the available data from controlled studies on the antiarrhythmic effects of magnesium, there are only a few types of diastolic arrhythmias, such as torsade de pointes, digitalis-induced ventricular arrhythmias and ventricular arrhythmias occurring in the presence of heart failure or during the perioperative state, in which the antiarrhythmic benefit of magnesium has been shown and/or established. Particularly in patients with one of these types of cardiac arrhythmias, however, it should be realized that preventing the patient from a magnesium deficit is the first, and the application of magnesium the second best strategy to keep the patient free from cardiac arrhythmias.

Effect of intravenous magnesium sulfate on cardiac arrhythmias in critically ill patients with low serum ionized magnesium

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Japanese Circulation Journal (Japan), 1996, 60/11 (871-875)

Magnesium affects cardiac function, although until the recent development of a new ion selective electrode no method existed for measuring the physiologically active form of magnesium, free ions (iMg²⁺), in the blood. We investigated the antiarrhythmic effect of magnesium sulfate administered to critically ill patients with cardiac arrhythmias and reduced iMg²⁺ as determined using the ion-selective electrode. Eight patients with a low iMg²⁺ level (less than 0.40 mmol/L) were given intravenous magnesium sulfate (group L). Magnesium sulfate was also administered to patients with a normal iMg²⁺ level (more than 0.40 mmol/L) but who did not

respond to conventional antiarrhythmic drugs (group N). Intravenous magnesium sulfate significantly increased the iMg²⁺ level in patients in group L from 0.35 plus or minus 0.06 mmol/L (mean plus or minus SD) to 0.54 plus or minus 0.09 mmol/L ($p < 0.01$), and had an antiarrhythmic effect in 7 of the 8 patients (88%). However, in group N patients, intravenous magnesium sulfate had an antiarrhythmic effect in only 1 of the 6 patients (17%) ($p < 0.05$ vs group L). These results suggest that intravenous magnesium sulfate may be effective in the acute management of cardiac arrhythmias in patients with a low serum iMg²⁺ level.

Ionic mechanisms of ischemia-related ventricular arrhythmias

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Clinical Cardiology (USA), 1996, 19/4 (325-331)

The aim of this review is the utmost simplification of the cellular electrophysiologic background of ischemia-related arrhythmias. In the acute and subacute phase of myocardial infarction, arrhythmias can be caused by an abnormal impulse generation, abnormal automaticity or triggered activity caused by early or delayed afterdepolarizations (EAD and DAD), or by abnormalities of impulse conduction (i.e., reentry). This paper addresses therapeutic intervention aimed at preventing the depolarization of 'pathologic' slow fibers, counteracting the inward calcium (Ca) influx that takes place through the L-type channels (Ca antagonists), or hyperpolarizing the diastolic membrane action potential increasing potassium (K) efflux (K-channel openers) in arrhythmias generated by an abnormal automaticity (ectopic tachycardias or accelerated idioventricular rhythms). If the cause of enhanced impulse generation is related to triggered activity, and since both EAD and DAD are dependent on calcium currents that can appear during a delayed repolarization, the therapeutic options are to shorten the repolarization phase through K-channel openers or Ca antagonists, or to suppress the inward currents directly responsible for the afterdepolarization with Ca blockers. Magnesium seems to represent a reasonable choice, as it is able to shorten the action potential duration and to function as a Ca antagonist. Abnormalities of impulse conduction (reentry) account for the remainder of arrhythmias that occur in the acute and subacute phase of ischemia and for most dysrhythmias that develop during the chronic phase. Reentrant circuits due to ischemia are usually Na channel-dependent. During choice will depend on the length of the excitable gap: in case of a short gap (ventricular fibrillation, polymorphic ventricular tachycardia, etc.), the refractory period has been identified as the most vulnerable parameter, and therefore a correct therapeutic approach will be based on drugs able to prolong the effective refractory period (K-channel blockers, such as class III antiarrhythmic drugs); on the other hand, for those arrhythmias characterized by a long excitable gap (most of the monomorphic ventricular tachycardias), the most appropriate therapeutic intervention consists of depressing ventricular excitability and conduction by use of sodium-channel blockers such as mexiletine and lidocaine. Compared with other class I antiarrhythmic agents, these drugs minimally affect refractoriness and exhibit a use-dependent effect and a voltage dependent action (i.e., more pronounced on the ischemic tissue because of its partial depolarization).

Myocardial infarction: The first 24 hours

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American Family Physician (USA), 1996, 54/3 (921-938)

Myocardial infarction is the most common cause of death in the United States. Rapid postinfarction intervention in the first 24 hours decreases mortality. Treatment modalities are rapidly evolving as new data from basic science research and clinical trials become available. Rapid thrombolysis, accurate criteria for diagnosis and administration of effective adjunctive therapy are crucial in preventing complications of myocardial infarction. Initial measures in the emergency department include intravenous access, accurate history and physical assessment, placement of oxygen, electrocardiography, use of aspirin and nitrates, and consideration of thrombolysis or angioplasty in appropriate candidates, optimally within one to two hours of myocardial infarction. After hospital admission, additional adjunctive treatment, including beta blockers, angiotensin-converting enzyme inhibitors and anticoagulation, can be instituted.

Proarrhythmic and antiarrhythmic actions of ion channel blockers on arrhythmias in the heart: Model study

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We explain why 1) some class I and IV antiarrhythmia drugs could exert proarrhythmic action, 2) some class III drugs are effective in controlling reentrant arrhythmias, and 3) cycle length (CL) oscillation is involved in the termination or initiation of reentry. To explain these phenomena, we employ the following three means: bifurcation analysis, simulation, and model construction. Antiarrhythmia drugs are modeled by varying maximal conductances of Na⁺, Ca²⁺, and time-dependent delayed rectifying and time-independent inward rectifying K channels in the Beeler-Reuter model, where the model cells are arranged in a ring. Bifurcation analysis predicts that there is a critical ring size (CRS) at which infinite ring behavior suddenly breaks down. Channel blockers can affect CRS in different manners: Na⁺ and Ca²⁺ blockers shorten CRS, whereas delayed rectifying K⁺ channel blockers and the inward K⁺ channel blockers lengthen CRS. This differential explains why some antiarrhythmia drugs are proarrhythmic (i.e., shorten CRS) whereas others are antiarrhythmic (i.e., lengthen CRS). Simulation is then used to investigate how the drugs affect reentrant rhythms in the neighborhood of the CRS. We find that, in this region, CL, conduction velocity, and action potential duration become oscillatory. As ring size shrinks, the pattern of the oscillation becomes more complex. When the ring shrinks to a certain size, reentry can no longer be sustained, and it terminates after a few oscillatory cycles. To explain the basic mechanism involved in CL oscillation, we then construct a minimal model that contains a low-threshold fast inward current and a high-threshold slow inward current. With this model, we show that the two inward currents, with vastly different activation and inactivation kinetics, cause CL oscillations. Our results thus give theoretical explanations for the experimental finding of Frame's group in canine atrial tricuspid ring in vitro that class IC drugs can bring about stable reentry from nonsustained transient reentry, whereas class III drugs transform stable reentry to complex oscillations in CL. Our results also support the result of Frame's group, in that, in 'adjustable' tricuspid rings, CL oscillation becomes more complex and its period becomes shorter as an excitable gap is shortened.

Prophylactic effects of taurine and diltiazem, alone or combined, on reperfusion arrhythmias in rats

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Acta Pharmacologica Sinica (China), 1996, 17/2 (122-124)

Aim: To study the effects of taurine (Tau) and diltiazem (Dil), alone or in combination, on reperfusion arrhythmias in anesthetized rats.

Methods: The arrhythmias were produced by coronary artery ligation for 15 min followed by reperfusion. Malondialdehyde (MDA) content and superoxide dismutase (SOD) activity were measured by thiobarbituric acid fluorescence assay and colorimetric determination.

Results: Taurine 70 mg . kg⁻¹ in combination with Dil 1 mg . kg⁻¹ were more effective on prevention of the reperfusion arrhythmias than each drug alone. The combination of both drugs not only decreased the content of MDA, but also increased the activity of SOD in reperfusion myocardium.

Conclusion: The inhibition of lipoperoxides formation as well as the inhibition of the calcium influx was involved in the antiarrhythmic effect of both taurine and diltiazem.

The cardiovascular protective role of docosahexaenoic acid

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European Journal of Pharmacology (Netherlands), 1996, 300/1-2 (83-89)

Dietary fish oils rich in n-3 polyunsaturated fatty acids can modulate a diverse range of factors contributing to cardiovascular disease. This study examined the relative roles of eicosapentaenoic acid (20:5 n-3; EPA) and docosahexaenoic acid (22:6 n-3; DHA) which are the principal n-3 polyunsaturated fatty acids regarded as candidates for cardioprotective actions. At low dietary intakes (0.4-1.1% of energy (%en)), docosahexaenoic acid but not eicosapentaenoic acid inhibited ischaemia-induced cardiac arrhythmias. At intakes of 3.9-10.0%en, docosahexaenoic acid was more effective than eicosapentaenoic acid at retarding hypertension development in spontaneously hypertensive rats (SHR) and inhibiting thromboxane-like vasoconstrictor responses in aortas from SHR. In stroke-prone SHR with established hypertension, docosahexaenoic acid (3.9-10.0%en) retarded the development of salt-loading induced proteinuria but eicosapentaenoic acid alone was ineffective. The results demonstrate that purified n-3 polyunsaturated fatty acids mimic the cardiovascular actions of fish oils and imply that docosahexaenoic acid may be

the principal active component conferring cardiovascular protection.

Trace elements in prognosis of myocardial infarction and sudden coronary death

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Journal of Trace Elements in Experimental Medicine (USA), 1996, 9/2 (57-62)

Ca, Cu, Mg, Mn, and Zn concentrates were measured in plasma, RBC, and hair of 350 men aged 40-59 years with myocardial infarction (MI) and/or who died from sudden cardiac death (SCD), as compared with normal controls. Analyses were done by flame atomic absorption spectrophotometry. Cu in plasma of MI patients was significantly higher than the controls'. Plasma Mn was significantly lower in SCD than in MI subjects. No other consistent and significant changes were observed. Past and present evidence indicates that high plasma Cu levels may be associated with heart failure and rhythm disorders. The low plasma Mn levels may be an indicator of decreased parasympathetic tonus thus favouring myocardial desynchronization and A-V block. Cu inhibits phosphodiesterase activity and Mn inhibits adenylate cyclase activity thus exerting an influence on the contractility of cardiomyocytes and of smooth muscle cells in coronary arteries. Cu and Mn analyses may thus have a prognostic significance for MI and SCD.

Prevention of cardiac arrhythmia by dietary (n-3) polyunsaturated fatty acids and their mechanism of action

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Australia

Journal of Nutrition (USA), 1997, 127/3 (383-393)

The role of marine fish oil (n-3) polyunsaturated fatty acids in the prevention of fatal ventricular arrhythmia has been established in experimental animals. Prevention of arrhythmias arising at the onset of ischemia and reperfusion is important because if untreated, they result in sudden cardiac death. Animals supplemented with fish oils in their diet developed little or no ventricular fibrillation after ischemia was induced. Similar effects have also been observed in cultured neonatal cardiomyocytes. Several mechanisms have been proposed and studied to explain the antiarrhythmic effects of fish oil polyunsaturated fatty acids, but to date, no definite mechanism has been validated. The sequence of action of these mechanisms and whether more than one mechanism is involved is also not clear. Some of the mechanisms suggested to explain the antiarrhythmic action of fish oils include the incorporation and modification of cell membrane structure by (n-3) polyunsaturated fatty acids, their direct effect on calcium channels and cardiomyocytes and their role in eicosanoid metabolism. Other mechanisms that are currently being investigated include the role of (n-3) polyunsaturated fatty acids in cell signalling mediated through phosphoinositides and their effect on various enzymes and receptors. This article reviews these mechanisms and the antiarrhythmic studies using (n-3) polyunsaturated fatty acids.

Exposure to the n-3 polyunsaturated fatty acid docosahexaenoic acid impairs alpha1-adrenoceptor-mediated contractile responses and inositol phosphate formation in rat cardiomyocytes

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Naunyn-Schmiedeberg's Archives of Pharmacology (Germany), 1996, 354/2 (109-119)

The beneficial effects of n-3 polyunsaturated fatty acids of fish oil in the prevention of fatal arrhythmias in myocardial ischemia were suggested to be at least in part mediated by a modulation of dihydropyridine-sensitive L-type calcium channels. As cardiac alpha1-adrenoceptor stimulation has been suggested to have no significant effect on L-type calcium channels, the aim of this study using cultured neonatal rat cardiomyocytes was to investigate whether chronic n-3 polyunsaturated fatty acid exposure may have an influence on alpha1-adrenoceptor-induced positive inotropic effects and induction of arrhythmias. Pretreatment of the rat cardiomyocytes for 3 days in the presence of the n-3 polyunsaturated fish oil-derived fatty acid docosahexaenoic acid (60 micromol/l) markedly decreased alpha1-adrenoceptor-stimulated increase in contraction velocity and induction of arrhythmias. The increase in contraction velocity of the cardiomyocytes induced by the beta-adrenoceptor agonist isoprenaline was also markedly reduced by the n-3 fatty acid pretreatment. Basal contractile amplitude and spontaneous beating frequency of the cardiomyocytes

were not significantly altered by the docosahexaenoic acid exposure. The pretreatment of the rat cardiomyocytes for 3 days in the presence of docosahexaenoic acid (60 micromol/l) decreased alpha1-adrenoceptor-stimulated formation of the calcium-mobilizing second messenger IP3 and its metabolites IP2 and IP1 by 55%. The depression of IP3 formation by docosahexaenoic acid treatment was not mediated by a decreased uptake of myo-inositol into the cardiomyocytes nor by a decreased synthesis of phosphatidylinositol bisphosphate (PIP2), the substrate of phospholipase C. The level of glycerol-3-phosphate, an important substrate of the phosphoinositide cycle, was unaltered by the docosahexaenoic acid pretreatment. Receptor binding studies revealed that the dissociation constant and maximal binding capacity of the alpha1-adrenoceptor antagonist (3H)prazosin was unchanged by the n-3 polyunsaturated fatty acid exposure. beta-Adrenoceptor- and forskolin-stimulated adenylyl cyclase activities were not diminished by the docosahexaenoic acid pretreatment. Chronic exposure of the cardiomyocytes to the n-6 polyunsaturated fatty acid arachidonic acid (60 micromol/l) did neither significantly alter alpha1-adrenoceptor-induced inositol phosphate formation nor alpha1-adrenoceptor-stimulated increase in contraction velocity. The results presented show that chronic n-3 polyunsaturated fatty acid pretreatment of rat cardiomyocytes leads to a marked impairment of alpha1-adrenoceptor-induced positive inotropic effects and induction of arrhythmias concomitant with a n-3 fatty acid-induced decrease in IP3 formation. This derangement of the phosphoinositide pathway by chronic n-3 fatty acid exposure may, thus, contribute to the beneficial effects of fish oil-derived fatty acids in the prevention of fatal arrhythmias in myocardial ischemia.

Selenium deficiency associated with cardiac dysfunction in three patients with chronic respiratory failure

To Y.; Koshino T.; Kubo M.; Yoshizawa A.; Kudo K.; Kabe J.
Japan
Japanese Journal of Thoracic Diseases (Japan), 1996, 34/12 (1406-1410)

We encountered three patients with chronic respiratory failure who had heart failure of cardiac arrhythmias and low levels of serum selenium. All three had tracheostomies and had received long-term parenteral nutrition that had not included selenium. All three also had refractory cardiac dysfunction, which was manifested in edema, heart failure, and various tachycardias. We suspected that selenium deficiency had caused their cardiac dysfunction. Serum selenium concentrations were found to be much lower than normal in all three, so 100 microg/day of selenium was administered in addition to their tube feedings. Cardiac function improved after replacement of selenium. These cases show the need for preventing selenium deficiency in patients with chronic respiratory failure during long-term administration of parenteral nutrition.

Fish oil and other nutritional adjuvants for treatment of congestive heart failure

McCarty M.F.
Medical Hypotheses (United Kingdom), 1996, 46/4 (400-406)

Published clinical research, as well as various theoretical considerations, suggest that supplemental intakes of the 'metavitamins' taurine, coenzyme Q10, and L-carnitine, as well as of the minerals magnesium, potassium, and chromium, may be of therapeutic benefit in congestive heart failure. High intakes of fish oil may likewise be beneficial in this syndrome. Fish oil may decrease cardiac afterload by an antivasopressor action and by reducing blood viscosity, may reduce arrhythmic risk despite supporting the heart's beta-adrenergic responsiveness, may decrease fibrotic cardiac remodeling by impeding the action of angiotensin II and, in patients with coronary disease, may reduce the risk of atherothrombotic ischemic complications. Since the measures recommended here are nutritional and carry little if any toxic risk, there is no reason why their joint application should not be studied as a comprehensive nutritional therapy for congestive heart failure.

Evidence on the participation of the 3',5'-cyclic AMP pathway in the non-genomic action of 1,25-dihydroxy-vitamin D3 in cardiac muscle.

Selles J; Boland R
Mol Cell Endocrinol (Netherlands) Dec 1991, 82 (2-3) p229-35

Several studies have suggested that vitamin D plays a role in cardiovascular function. It has been recently shown that in vitro treatment of vitamin D-deficient chick cardiac muscle with physiological concentrations of 1,25-dihydroxy-vitamin D3 (1,25(OH)2D3) induces a rapid (1-10 min) increase of tissue ⁴⁵Ca uptake which can be suppressed by Ca channel blockers. The hormone simultaneously stimulated heart microsomal membrane protein phosphorylation. Experiments were performed to investigate the

existence of a relationship between these changes and to obtain information about the mechanism involved in 1,25(OH)₂D₃-induced modifications in cardiac protein phosphorylation. Dibutyl cyclic AMP (10 microM) and forskolin (10 microM), known activators of the cAMP pathway, produced time courses of changes in ⁴⁵Ca uptake by chick heart tissue similar to 1,25(OH)₂D₃ (10(-10) M). Analogously to the hormone, the effects of both compounds were abolished by nifedipine (30 microM) and verapamil (10 microM). In agreement with these observations, 1,25(OH)₂D₃ significantly increased (34-70%) heart muscle cAMP levels within 1-10 min of treatment. In addition, 1,25(OH)₂D₃ and forskolin caused similar changes in cardiac microsomal membrane protein phosphorylation (e.g. stimulation in 43 kDa and 55 kDa proteins). These changes were also evidenced by direct exposure of isolated heart microsomes to 1,25(OH)₂D₃, suggesting a direct membrane action of the hormone. The fast effects of 1,25(OH)₂D₃ on dihydropyridine-sensitive cardiac muscle Ca uptake could be reproduced in primary-cultured myocytes isolated from chick embryonic heart. Furthermore, the effects of the hormone could be suppressed by a specific protein kinase A inhibitor. These results suggest that 1,25(OH)₂D₃ affects heart cell calcium metabolism through regulation of Ca channel activity mediated by the cAMP pathway.

1,25(OH)₂ vitamin D₃, and retinoic acid antagonize endothelin-stimulated hypertrophy of neonatal rat cardiac myocytes.

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Department of Medicine, University of California, San Francisco, 94143, USA.
J Clin Invest (United States) Apr 1 1996, 97 (7) p1577-88

1,25(OH)₂ Vitamin D₃ (VD₃) and retinoic acid (RA) function as ligands for nuclear receptors which regulate transcription. Though the cardiovascular system is not thought to represent a classical target for these ligands, it is clear that both cardiac myocytes and vascular smooth muscle cells respond to these agents with changes in growth characteristics and gene expression. In this study we demonstrate that each of these ligands suppresses many of the phenotypic correlates of endothelin-induced hypertrophy in a cultured neonatal rat cardiac ventriculocyte model. Each of these agents reduced endothelin-stimulated ANP secretion in a dose-dependent fashion and the two in combination proved to be more effective than either agent used alone (VD₃: 49%; RA:52%; VD₃ + RA:80% inhibition). RA, at concentrations known to activate the retinoid X receptor, and, to a lesser extent, VD₃ effected a reduction in atrial natriuretic peptide, brain natriuretic peptide, and alpha-skeletal actin mRNA levels. Similar inhibition (VD₃:30%; RA:33%; VD₃ + RA:59% inhibition) was demonstrated when cells transfected with reporter constructs harboring the relevant promoter sequences were treated with VD₃ and/or RA for 48 h. These effects were not accompanied by alterations in endothelin-induced c-fos, c-jun, or c-myc gene expression, suggesting either that the inhibitory locus responsible for the reduction in the mRNA levels lies distal to the activation of the immediate early gene response or that the two are not mechanistically coupled. Both VD₃ and RA also reduced [³H]leucine incorporation (VD₃:30%; RA:33%; VD₃ + RA:45% inhibition) in endothelin-stimulated ventriculocytes and, once again, the combination of the two was more effective than either agent used in isolation. Finally, 1,25(OH)₂ vitamin D₃ abrogated the increase in cell size seen after endothelin treatment. These findings suggest that the liganded vitamin D and retinoid receptors are capable of modulating the hypertrophic process in vitro and that agents acting through these or similar signaling pathways may be of value in probing the molecular mechanisms underlying hypertrophy.

[Effect of vitamin E deficiency on the development of cardiac arrhythmias as affected by acute ischemia]

Belkina LM; Arkhipenko IuV; Dzhaparidze LM; Saltykova VA; Meerson FZ
Biull Eksp Biol Med (USSR) Nov 1986, 102 (11) p530-2

Malonic dialdehyde content was increased by 53% in the myocardium of male Wistar rats (250-300 g) devoid of vitamin E for 2 months, as compared to the control rats (animals receiving an optimal amount of vitamin E). Transitory ischemia (10 min) with subsequent reoxygenation (5 min) was induced during open heart surgery under urethan anesthesia. Ischemia was induced by the occlusion of the descending branch of the left coronary artery. In ischemic rats with vitamin E deficiency the incidence of ventricular fibrillation, tachycardia, extrasystoles and the additive duration of arrhythmias were significantly increased as compared to the control.

Antioxidant protection against adrenaline-induced arrhythmias in rats with chronic heart hypertrophy.

Effects of vitamin E on adrenaline-induced arrhythmias were examined in rats with chronic heart hypertrophy subsequent to narrowing of the abdominal aorta. After 60 weeks of pressure overload, the rats showed an increase of about 21% in heart/body weight ratio and a small but significant rise in left ventricular end diastolic pressure (LVEDP) (sham control 1.7 +/- 0.67 mmHg; hypertrophy 7.1 +/- 2.7 mmHg) without any change in left ventricular peak systolic pressure (LVSP). Intravenous infusion of adrenaline caused rhythm disorders in a dose-dependent manner and pathological arrhythmias (occurrence of six premature ventricular complexes/min) were observed at doses of 2.9 +/- 0.6 and 3.8 +/- 1.0 micrograms/kg of the drug in control and hypertrophy animals, respectively. Administration of two doses of vitamin E (50 mg/kg intraperitoneally), given 24 h and 1 h before adrenaline infusion, significantly increased the amount of adrenaline required to produce pathological arrhythmias (control 8.0 +/- 3.0; hypertrophy 7.7 +/- 2.0 micrograms/kg). Vitamin E pretreatment did not have any detrimental effect on the pressure readings nor did it have any influence on adrenaline-induced pressure changes. The data suggest that a combination therapy with vitamin E may allow therapeutic use of higher concentrations of adrenaline required to improve function in failing hearts with a reduced risk of arrhythmias

The antiarrhythmic effects of taurine alone and in combination with magnesium sulfate on ischemia/reperfusion arrhythmia

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Chinese Pharmacological Bulletin (China), 1994, 10/5 (358-362)

The effect of taurine (Taur) alone and in combination with magnesium sulfate (MgSO₄) on ischemia/reperfusion arrhythmia was investigated. The arrhythmia was produced by coronary artery occlusion for 10 min followed by reperfusion. In addition, the present study also observed the effect of MgSO₄ alone and in combination with Taur on hemodynamics. The results showed that Taur (50 mg . kg⁻¹) and MgSO₄ (25 mg . kg⁻¹) had partly antiarrhythmic effect. Taur (100, 150mg. kg⁻¹) MgSO₄ (50, 100mg. kg⁻¹) had significantly antiarrhythmic effect. Taur (50 mg. kg⁻¹) combined with MgSO₄ (25 mg. kg⁻¹) shortened the duration of ventricular tachycardia (VT) more than that either drug did alone. The hypotensive effect of MgSO₄ (25 mg. kg⁻¹) was not increased by coadministration of Taur, but the myocardial oxygen consumption was reduced. These findings indicate that Taur in combination with MgSO₄ is more effective on reperfusion arrhythmia, and that the mechanism of antiarrhythmic effect of Taur and MgSO₄ may be involved in the effect of defence on myocardium.

The effects of antioxidants on reperfusion dysrhythmias

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Ceska a Slovenska Farmacie (Czech Republic), 1995, 44/5 (257-260)

The present study aims to investigate the effects of the lipophilic antioxidant Trolox C (a vitamin E analogue) and stobadine, a scavenger of free oxygen radicals, on reperfusion dysrhythmias. Experiments were performed on isolated perfused rat hearts subjected to global stop-flow ischaemia followed by reperfusion. Trolox C (10⁻⁴ mol.l⁻¹) and stobadine (10⁻⁵ mol.l⁻¹) were infused immediately prior to ischaemia. Trolox C (10⁻⁴ mol.l⁻¹) and stobadine (10⁻⁵ mol.l⁻¹) decreased the incidence and duration of reperfusion-induced dysrhythmias (quantified by the dysrhythmia score) in comparison to the ischaemic-reperfusion damaged hearts. There was an improvement in the recovery of contraction force and left ventricular diastolic pressure in Trolox or stobadine pretreated hearts. No significant changes in coronary flow resistance were observed. The results suggest that both substances protect the myocardium during ischaemic-reperfusion injury probably by affecting the generation and activity of reactive oxygen species.

Protective effects of all-trans-retinoic acid against cardiac arrhythmias induced by isoproterenol, lysophosphatidylcholine or ischemia and reperfusion

Kang JX; Leaf A

Previous studies have shown that free polyunsaturated fatty acids (PUFA) reduce the excitability of cardiac myocytes and exert antiarrhythmic effects. Therefore, we hypothesized that retinoic acid (RA, vitamin A acid), which has structural characteristics similar to those of PUFA, may have similar antiarrhythmic effects. To test this hypothesis, we used an isolated, spontaneously beating, neonatal rat cardiac myocyte preparation to examine the effects of RA, added to the perfusion solution, on the cell contraction and arrhythmias induced by isoproterenol (ISO) or lysophosphatidylcholine (LPC). All-trans-RA (10-20 microM) induced a marked and reversible reduction in the contraction rate of the cell in 2-5 min without changing the amplitude of the contractions. Superfusion of the myocytes with either ISO (3 microM) or LPC (5 microM) induced sustained tachyarrhythmias characterized by spasmodic contractures and fibrillation. Addition of 15-20 microM all-trans-RA to the perfusion solution effectively prevented as well as terminated the arrhythmias induced by ISO and LPC. Furthermore, in a whole-animal model of arrhythmia in which the left anterior descending coronary artery (LAD) of the anesthetized rat was occluded for 15 min followed by reperfusion, both the incidence and severity of ventricular tachycardia and fibrillation (VT, VF) were significantly reduced during the ischemic and reperfusion periods by intravenous infusion of all-trans-RA. In contrast, other analogues, including retinol and retinal, and other fat-soluble vitamins, including vitamin D, E, and K, did not have such effects. Our results demonstrate that all-trans-RA can produce antiarrhythmic effects similar to those of PUFA, suggesting a novel role of RA as a potential antiarrhythmic agent.

Effects of dietary supplementation with alpha-tocopherol on myocardial infarct size and ventricular arrhythmias in a dog model of ischemia-reperfusion

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J. Am. Coll. Cardiol. (USA), 1994, 24/6 (1580-1585)

Objectives. We investigated whether dietary supplementation with the antioxidant vitamin alpha-tocopherol (500 mg daily) might reduce lethal ventricular arrhythmias and infarct size.

Background. Previous studies suggested that dietary supplementation with alpha-tocopherol may be associated with a reduced risk of ischemic heart disease. However, the mechanism of this protection remains unknown.

Methods. Beagle dogs were randomized to either a supplemented or a control group. Because of the low mortality rate in the supplemented group, five dogs were added to the control group. After 2 months, dogs were anesthetized and underwent a 2-h coronary artery occlusion and 6-h reperfusion. Plasma vitamin E, retinol and malondialdehyde concentrations were assessed in all dogs.

Results. Fourteen dogs (11 of 25 control vs. 3 of 19 supplemented dogs, $p < 0.05$) developed ventricular fibrillation during either ischemia or reperfusion. Malondialdehyde concentrations were higher in dogs that subsequently developed arrhythmias (2.7 plus or minus 0.2 micromol/liter, mean plus or minus SEM) compared with dogs that did not (2.1 plus or minus 0.2 micromol/liter, $p = 0.03$). Among survivors with significant ischemia, infarct size was larger in supplemented ($n = 12$, 58.5 plus or minus 3.3% of area at risk) than in control ($n = 11$, 41.9 plus or minus 6.5%, $p < 0.04$) dogs. In addition, for a given collateral flow, supplemented dogs ($n = 16$) developed larger infarct size than control dogs ($n = 15$, $p < 0.001$, analysis of covariance).

Conclusions. The data suggest that dietary alpha-tocopherol supplementation prevented lethal ventricular arrhythmias associated with ischemia and reperfusion. However, its influence on infarct size and long-term prognosis warrants further investigation.

Magnesium flux during and after open heart operations in children.

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Department of Cardiothoracic Surgery, Killingbeck Hospital, Leeds, United Kingdom.
Ann Thorac Surg (United States) Apr 1995, 59 (4) p921-7

Hypomagnesemia and depletion of the body's magnesium stores is known to be associated with an increased incidence of both cardiac arrhythmias and neurological irritability. In a two-part prospective study we have evaluated whether magnesium deficiency is a significant occurrence in children treated in the intensive care unit after open heart operations, and subsequently have sought to identify how intraoperative metabolic changes were related to the resultant findings. In 41 children studied after operation the plasma magnesium concentration showed a significant decrease from 0.92 mmol/L (10th to 90th centile, 0.71 to 1.15 mmol/L)

immediately after operation to 0.77 mmol/L (0.65 to 0.91 mmol/L) on the following morning. The subsequent change in grouped values was not significant but 14 (34.2%) and 7 (17.1%) possessed values of less than 0.7 mmol/L and 0.6 mmol/L, respectively. The occurrence of cardiac arrhythmias was not statistically related to the occurrence of hypomagnesemia. In 21 children perioperative changes in extracellular and tissue magnesium, potassium, and calcium content were measured. It was found that hemodilution with a prime low in magnesium caused a reduction from a median of 0.81 mmol/L to 0.61 mmol/L ($p < 0.01$). Plasma potassium level, however, was elevated from 3.7 mmol/L to 4.15 mmol/L ($p < 0.05$) and the ionized calcium content from 1.17 mmol/L (1.07 to 1.25 mmol/L) to 1.49 mmol/L (1.25 to 2.56 mmol/L) ($p = 0.0009$). The myocardial content of magnesium did not change significantly but skeletal muscle content was depleted from 6.75 mmol/g (2.85 to 8.35 mmol/g) to 5.65 mmol/g (2.45 to 7.2 mmol/g) ($p < 0.01$)

Sino-atrial Wenckebach conduction in thyrotoxic periodic paralysis: a case report.

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Int J Cardiol (Ireland) Jan 6 1995, 47 (3) p285-9

A 28-year-old male presented with thyrotoxic periodic paralysis. On admission to hospital the serum potassium level was 1.4 mmol/l. The ECG showed classical features of hypokalaemia. In addition, sino-atrial block with Wenckebach conduction was also present. With the normalization of the serum potassium, the ECG became completely normal and showed no evidence of any arrhythmia .

A possible beneficial effect of selenium administration in antiarrhythmic therapy.

Lehr D

New York Medical College, N.Y. 10025-6421.

J Am Coll Nutr (United States) Oct 1994, 13 (5) p496-8

OBJECTIVE: The following review of the literature on the importance of Selenium (Se) in myocardial homeostasis and of the pharmacology of this trace metal, represents an attempt to search, without prejudice to other possible explanations, for a rationale of a beneficial effect of Se substitution as an adjuvant to antiarrhythmic therapy.

BACKGROUND: For several years, in the early 1980s, I had to deal with the problem of a serious ventricular arrhythmia (non-sustained and sustained ventricular tachycardia) which was remarkably resistant to a battery of the most potent antiarrhythmic agents. Eventually, dramatic improvement, lasting for a period of 8 years, was achieved with Flecainide, which, however, left unsolved the episodic occurrence of disabling ventricular bigemini. Over the most recent period of 1 year and 8 months, there was a sudden and unexplained return to unbroken normal sinus rhythm. Among the multiplicity of possible reasons for this fortunate development, the concurrent introduction of Se substitution appeared as the most obvious, though very tentative explanation. Substitution of this trace metal preceded the extinction of ventricular bigemini by 1 week and actually represented the sole modification of otherwise reasonably standardized conditions of antiarrhythmic therapy, life style and diet. (25 Refs.)

Omega-3 fatty acids and prevention of ventricular fibrillation.

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Prostaglandins Leukot Essent Fatty Acids 1995 Feb-Mar;52(2-3):197-8

Interest in the potential cardiovascular benefits of omega-3 long chain polyunsaturated fatty acids has been largely focused on possible antiatherothrombotic effects. In addition, however, definitive antiarrhythmic effects of these dietary omega-3 fatty acids have been reported by Charnock & McLennan. Our studies commenced with the observation that two of these fatty acids, eicosapentaenoic (C20:5n-3, EPA) and docosahexaenoic acid (C22:6n-3, DHA) prevented contracture and fibrillation of isolated neonatal cardiac myocytes when exposed to toxic levels of ouabain (0.1 mM). This protection was associated with prevention of excessively high intracellular calcium concentrations in the myocyte. Further, it was shown that these fatty acids modulate calcium currents through L-type calcium channels and that the effect occurs within a few minutes of adding EPA or DHA to the medium perfusing the cultured cardiac myocytes. Infusing an emulsion of the omega-3 fatty acids intravenously just prior to compression of a coronary artery in a conscious, prepared dog will prevent the expected subsequent ischemia-induced ventricular

[Effect of anti-arrhythmia drugs on the beta2 receptor-dependent adenylyl cyclase system of lymphocytes in patients with cardiac rhythm disorders]

Krasnikova TL, Iurkova VB, Ku'zmina MM, Ku'lginskaia IV, Sokolov SF, Golitsyn SI, Chernousova TV, Svet EA, Mazaev AV
Kardiologiia (USSR) Jul 1989, 29 (7) p25-9

The authors analyzed the density of beta 2-adrenoreceptors, their affinity for catecholamines and activity of peripheral lymphocyte adenylyl cyclase in healthy donors and patients with frequent ventricular premature contraction (VPC) in their pretreatment state and during short-term ethmosine or allapinine therapy. The density of beta 2-adrenoreceptors was increased by 43%, whereas guanylimidodiphosphate- or forskolin-induced stimulation of adenylyl cyclase was decreased in the lymphocytes of VPC patients as compared to those of healthy donors. Ethmosine therapy failed to produce any changes in the density and affinity of the receptors for catecholamines. Allapinine caused a 47% reduction in beta 2-adrenoreceptor density and a 10(2)-10(3)-fold decrease in receptor affinity for 1-isoproterenol. After discontinuation of allapinine, the changes in beta 2-adrenoreceptor density and affinity for catecholamines remained on days 3 and 7, respectively. The clinical effect of both ethmosine and allapinine was accompanied by an increase in lymphocyte adenylyl cyclase activity.

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ARRHYTHMIA (CARDIAC)

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- > Effect of coenzyme Q10 on structural alterations in the renal membrane of stroke-prone spontaneously hypertensive rats.
- > Co-enzyme Q10: a new drug for cardiovascular disease.
- > [Effects of 2,3-dimethoxy-5-methyl-6-(10'-hydroxydecyl)-1,4-benzoquinone (CV-2619) on adriamycin-induced ECG abnormalities and myocardial energy metabolism in spontaneously hypertensive rats]
- > Bioenergetics in clinical medicine. III. Inhibition of coenzyme Q10-enzymes by clinically used anti-hypertensive drugs.
- > Bioenergetics in clinical medicine. Studies on coenzyme Q10 and essential hypertension.
- > [Prevention of cerebrovascular insults]
- > [Essential antioxidants in cardiovascular diseases--lessons for Europe]

- > Antioxidant vitamin intake and coronary mortality in a longitudinal population study.
 - > The decline in stroke mortality. An epidemiologic perspective.
 - > Can antioxidants prevent ischemic heart disease?
 - > Antioxidant therapy in the aging process.
 - > Effect of flosequinan on ischaemia-induced arrhythmias and on ventricular cyclic nucleotide content in the anaesthetized rat.
 - > What do the newer inotropic drugs have to offer?
 - > Arrhythmogenic effect of forskolin in the isolated perfused rat heart: Influence of nifedipine reduction of external calcium
 - > Hormone secretagogues increase cytosolic calcium by increasing cAMP in corticotropin-secreting cells
 - > The genesis of arrhythmias during myocardial ischemia. Dissociation between changes in cyclic adenosine monophosphate and electrical instability in the rat
 - > Effects of high K on relaxation produced by drugs in the guinea-pig tracheal muscle
 - > Forskolin inhibits ouabain-sensitive ATPase in the medulla of rat kidney
-

An expanded concept of "insurance" supplementation--broad-spectrum protection from cardiovascular disease.

McCarty MF
Med Hypotheses (England) Oct 1981, 7 (10) p1287-1302

The preventive merits of "nutritional insurance" supplementation can be considerably broadened if meaningful doses of nutrients such as mitochondrial "metavitamins" (coenzyme Q, lipoic acid, carnitine), lipotropes, and key essential fatty acids, are included in insurance supplements. From the standpoint of cardiovascular protection, these nutrients, as well as magnesium, selenium, and GTF-chromium, appear to have particular value. Sophisticated insurance supplementation would likely have a favorable impact on many parameters which govern cardiovascular risk--serum lipid profiles, blood pressure, platelet stability, glucose tolerance, bioenergetics, action potential regulation--and as a life-long preventive health strategy might confer substantial benefit. (111 Refs.)

Italian multicenter study on the safety and efficacy of coenzyme Q10 as adjunctive therapy in heart failure (interim analysis)

Baggio E, Gandini R, Plancher AC, Passeri M, Carmosino G
Department of Internal Medicine, V. Buzzi Hospital, Milan.
Clin Investig (Germany) 1993, 71 (8 Suppl) pS145-9

Digitalis, diuretics, and vasodilators are considered standard therapy for patients with congestive heart failure, for which treatment is tailored according to the severity of the syndrome and the patient profile. Apart from the clinical seriousness, heart failure is always characterized by an energy depletion status, as indicated by low intramyocardial ATP and coenzyme Q10 levels. We investigated safety and clinical efficacy of coenzyme Q10 (CoQ10) adjunctive treatment in congestive heart failure, which had been diagnosed at least 6 months previously and treated with standard therapy. A total of 2500 patients in NYHA classes II and III were enrolled in this open noncomparative 3-month postmarketing drug surveillance study in 173 Italian centers. The daily dose of CoQ10 was 50-150 mg orally, with the majority of patients (78%) receiving 100 mg/day. Clinical and laboratory parameters were evaluated at the entry into the study and on day 90; the assessment of clinical signs and symptoms was made using from two- to seven-point scales. Preliminary results on 1113 patients (mean age 69.5 years) show a low incidence of side effects: 10 adverse reactions were reported in 8 (0.8%) patients, of which only 5 reactions were considered as correlated to the test treatment. After 3 months of test treatment the proportions of patients with improvement in clinical signs and symptoms were as follows: cyanosis 81%, edema 76.9%, pulmonary rales 78.4%, enlargement of the liver area 49.3%, jugular reflux 81.5%, dyspnea 54.2%, palpitations 75.7%, sweating 82.4%, arrhythmia 62%, insomnia 60.2%, vertigo 73%, and nocturia 50.7%.

Isolated diastolic dysfunction of the myocardium and its response to CoQ10 treatment.

Langsjoen PH, Langsjoen PH, Folkers K
Clin Investig (Germany) 1993, 71 (8 Suppl) pS140-4

Symptoms of fatigue and activity impairment, atypical precordial pain, and cardiac arrhythmia frequently precede by years the development of congestive heart failure. Of 115 patients with these symptoms, 60 were diagnosed as having hypertensive cardiovascular disease, 27 mitral valve prolapse syndrome, and 28 chronic fatigue syndrome. These symptoms are common with diastolic dysfunction, and diastolic function is energy dependent. All patients had blood pressure, clinical status, coenzyme Q10 (CoQ10) blood levels and echocardiographic measurement of diastolic function, systolic function, and myocardial thickness recorded before and after CoQ10 replacement. At control, 63 patients were functional class III and 54 class II; all showed diastolic dysfunction; the mean CoQ10 blood level was 0.855 micrograms/ml; 65%, 15%, and 7% showed significant myocardial hypertrophy, and 87%, 30%, and 11% had elevated blood pressure readings in hypertensive disease, mitral valve prolapse and chronic fatigue syndrome respectively. Except for higher blood pressure levels and more myocardial thickening in the hypertensive patients, there was little difference between the three groups. CoQ10 administration resulted in improvement in all; reduction in high blood pressure in 80%, and improvement in diastolic function in all patients with follow-up echocardiograms to date; a reduction in myocardial thickness in 53% of hypertensives and 36% of the combined prolapse and fatigue syndrome groups; and a reduced fractional shortening in those high at control and an increase in those initially low. (ABSTRACT TRUNCATED AT 250 WORDS)

Protective effects of propionyl-L-carnitine during ischemia and reperfusion.

Shug A, Paulson D, Subramanian R, Regitz V
University of Wisconsin Medical School, Madison.
Cardiovasc Drugs Ther (United States) Feb 1991, 5 Suppl 1 p77-83

When cardiac function in isolated rat hearts was impaired by subjecting them to ischemia, subsequent perfusion with propionyl-L-carnitine and related compounds increased their rate of recovery. Thus at 11 mM, both propionyl-L-carnitine and, to a lesser extent, its taurine amide, and also acetyl-L-carnitine, significantly restored cardiac function in 15 minutes after 90 minutes of either low-flow or intermittent no-flow ischemia. Carnitine itself was ineffective. Propionyl-L-carnitine also increased tissue ATP and creatine phosphate compared with controls, but did not affect the levels of long-chain acyl carnitine and coenzyme. These esters also depleted fatty acid peroxidation, as shown with malonaldehyde, and were more effective than carnitine in preventing the production of superoxide. In myocytes, propionyl-L-carnitine alone stimulated palmitate oxidation, but in rat heart homogenates, both L-carnitine and propionyl-L-carnitine did so, while acetyl-L-carnitine was actually inhibitory. Possible mechanisms for the protective action of propionyl-L-carnitine against ischemia include an increased rate of cellular transport, stimulation of fatty acid oxidation, and a reduction of free radical formation.

Consequences of magnesium deficiency on the enhancement of stress reactions; preventive and therapeutic implications (a review).

Seelig MS

Stress intensifies release of catecholamines and corticosteroids that increase survival of normal animals when their lives are threatened. When magnesium (Mg) deficiency exists, stress paradoxically increases risk of cardiovascular damage including hypertension, cerebrovascular and coronary constriction and occlusion, arrhythmias and sudden cardiac death (SCD). In affluent societies, severe dietary Mg deficiency is uncommon, but dietary imbalances such as high intakes of fat and/or calcium (Ca) can intensify Mg inadequacy, especially under conditions of stress. Adrenergic stimulation of lipolysis can intensify its deficiency by complexing Mg with liberated fatty acids (FA). A low Mg/Ca ratio increases release of catecholamines, which lowers tissue (i.e. myocardial) Mg levels. It also favors excess release or formation of factors (derived both from FA metabolism and the endothelium), that are vasoconstrictive and platelet aggregating; a high Ca/Mg ratio also directly favors blood coagulation, which is also favored by excess fat and its mobilization during adrenergic lipolysis. Auto-oxidation of catecholamines yields free radicals, which explains the enhancement of the protective effect of Mg by anti-oxidant nutrients against cardiac damage caused by beta-catecholamines. Thus, stress, whether physical (i.e. exertion, heat, cold, trauma--accidental or surgical, burns), or emotional (i.e. pain, anxiety, excitement or depression) and dyspnea as in asthma increases need for Mg. Genetic differences in Mg utilization may account for differences in vulnerability to Mg deficiency and differences in body responses to stress.

Community-based prevention of stroke: nutritional improvement in Japan

Yamori Y, Horie R
Kyoto University, Japan.
Health Rep 1994;6(1):181-8

OBJECTIVES: (1) To demonstrate the importance of nutrition, especially sodium restriction and increased potassium and protein intakes, in the prevention of hypertension and stroke in a pilot study involving senior citizens. (2) To design a population-based intervention in the Shimane Prefecture of Japan concerning dietary factors such as low sodium and high potassium, protein, magnesium, calcium and dietary fibre in the prevention of stroke.

DESIGN AND METHODS: The intervention study was carried out at a senior citizens' residence and included general health education along with a reduction of dietary salt intake and increases in vegetable and protein, especially from seafood. Sixty-three healthy senior citizens (average age: 74.8 +/- 7.7 years) had their daily meals modified to a low sodium/potassium ratio for four weeks without their knowledge by the use of a potassium chloride substitute for salt, soy sauce and bean paste, which contains much less sodium and more potassium. Monosodium L-glutamate monohydrate used for cooking was changed to monopotassium L-glutamate monohydrate. Blood pressure was measured with the patient in the sitting position. Daily dietary sodium and potassium intakes were assessed by flame photometry from 24-hour urine specimens. Extensive intervention programs were introduced into the Shimane Prefecture, which has a population of 750,000, through health education classes for housewives, home visits by health nurses and an educational TV program for dietary improvement. The mortality from stroke was monitored for 10 years and compared with the average in Japan.

RESULTS: The blood pressure lowering effect of reducing the dietary sodium/potassium ratio was confirmed through a pilot intervention study at the senior citizens' residence. The mortality rates for stroke in the middle-aged population from the Shimane Prefecture during the 10 years after the introduction of dietary improvement had a steeper decline in hemorrhagic, ischemic and all strokes than the average for Japan.

Effect of dietary magnesium supplementation on intralymphocytic free calcium and magnesium in stroke-prone spontaneously hypertensive rats.

Adachi M; Nara Y; Mano M; Yamori Y
Department of Pathology, Shimane Medical University, Izumo, Japan.
Clin Exp Hypertens 1994 May;16(3):317-26

The effects of dietary magnesium (Mg) supplementation on intralymphocytic free Ca^{2+} ($[Ca^{2+}]_i$) and Mg^{2+} ($[Mg^{2+}]_i$) were examined in the stroke-prone spontaneously hypertensive rats (SHRSP) at the age of 10 weeks. After 40 day Mg supplementation (0.8% Mg in the diet), systolic blood pressure (SBP) was significantly lower in Mg supplemented group (Mg group) than the control group (0.2% Mg). $[Ca^{2+}]_i$ was significantly lower and $[Mg^{2+}]_i$ was significantly higher in Mg group than in the control group. Further, $[Ca^{2+}]_i$ was positively and $[Mg^{2+}]_i$ was negatively correlated with SBP. These results suggest that dietary Mg supplementation modifies $[Ca^{2+}]_i$ and $[Mg^{2+}]_i$, and modulates the development of hypertension.

Clinical study of cardiac arrhythmias using a 24-hour continuous electrocardiographic recorder (5th report)--antiarrhythmic action of coenzyme Q10 in diabetics.

Fujioka T, Sakamoto Y, Mimura G
Tohoku J Exp Med (Japan) Dec 1983, 141 Suppl p453-63

An investigation was undertaken to evaluate the antiarrhythmic effect of CoQ10 on VPBs using the Holter ECG, in 27 patients with no clinical findings of organic cardiopathies. As a result, the effect of CoQ10 on VPBs was considered beneficial in 6 (22%) of 27 cases, consisting of 1 patient with hypertension and 5 patients with DM. Even in the remaining 2 patients with DM, the frequency of VPBs was reduced by 50% or more during treatment with CoQ10. The mean reduction of VPBs frequency in the 5 responders plus these 2 patients with DM was 85.7%. These findings suggest that CoQ10 exhibits an effective antiarrhythmic action not merely on organic heart disease but also on VPBs supervening on DM.

Usefulness of coenzyme Q10 in clinical cardiology: a long-term study.

Langsjoen H, Langsjoen P, Langsjoen P, Willis R, Folkers K
University of Texas Medical Branch, Galveston 77551, USA.
Mol Aspects Med 1994;15 Suppl:s165-75

Over an eight year period (1985-1993), we treated 424 patients with various forms of cardiovascular disease by adding coenzyme Q10 (CoQ10) to their medical regimens. Doses of CoQ10 ranged from 75 to 600 mg/day by mouth (average 242 mg). Treatment was primarily guided by the patient's clinical response. In many instances, CoQ10 levels were employed with the aim of producing a whole blood level greater than or equal to 2.10 micrograms/ml (average 2.92 micrograms/ml, n = 297). Patients were followed for an average of 17.8 months, with a total accumulation of 632 patient years. Eleven patients were omitted from this study: 10 due to non-compliance and one who experienced nausea. Eighteen deaths occurred during the study period with 10 attributable to cardiac causes. Patients were divided into six diagnostic categories: ischemic cardiomyopathy (ICM), dilated cardiomyopathy (DCM), primary diastolic dysfunction (PDD), hypertension (HTN), mitral valve prolapse (MVP) and valvular heart disease (VHD). For the entire group and for each diagnostic category, we evaluated clinical response according to the New York Heart Association (NYHA) functional scale, and found significant improvement. Of 424 patients, 58 per cent improved by one NYHA class, 28% by two classes and 1.2% by three classes. A statistically significant improvement in myocardial function was documented using the following echocardiographic parameters: left ventricular wall thickness, mitral valve inflow slope and fractional shortening. Before treatment with CoQ10, most patients were taking from one to five cardiac medications. During this study, overall medication requirements dropped considerably: 43% stopped between one and three drugs. Only 6% of the patients required the addition of one drug. No apparent side effects from CoQ10 treatment were noted other than a single case of transient nausea. In conclusion, CoQ10 is a safe and effective adjunctive treatment for a broad range of cardiovascular diseases, producing gratifying clinical responses while easing the medical and financial burden of multidrug therapy.

Effect of coenzyme Q10 on structural alterations in the renal membrane of stroke-prone spontaneously hypertensive rats.

Okamoto H, Kawaguchi H, Togashi H, Minami M, Saito H, Yasuda H
Department of Cardiovascular, Hokkaido University, Japan.
Biochem Med Metab Biol 1991 Apr;45(2):216-26

To test the hypothesis that structural abnormalities exist in the kidney membrane of spontaneously hypertensive rats, we examined the effect of long-term administration of coenzyme Q10 on membrane lipid alterations in the kidney of stroke-prone spontaneously hypertensive rats (SHRSP). As compared with normotensive Wistar-Kyoto rats, renal membrane phospholipids, especially phosphatidylcholine and phosphatidylethanolamine, decreased and renal phospholipase A2 activity was enhanced with age in untreated SHRSP. Treatment with coenzyme Q10 attenuated the elevation of blood pressure, the membranous phospholipid degradation, and the enhanced phospholipase A2 activity. These results suggest that one factor contributing to the progress of hypertension is a structural membrane abnormality that alters the physical and functional properties of the cell membrane, and coenzyme Q10 might protect the renal membrane from damage due to hypertension in SHRSP.

Co-enzyme Q10: a new drug for cardiovascular disease.

Greenberg S, Frishman WH

Department of Medicine, Mt. Sinai Hospital and Medical Center, New York, New York.

J Clin Pharmacol 1990 Jul;30(7):596-608

Co-enzyme Q10 (ubiquinone) is a naturally occurring substance which has properties potentially beneficial for preventing cellular damage during myocardial ischemia and reperfusion. It plays a role in oxidative phosphorylation and has membrane stabilizing activity. The substance has been used in oral form to treat various cardiovascular disorders including angina pectoris, hypertension, and congestive heart failure. Its clinical importance is now being established in clinical trials worldwide.

[Effects of 2,3-dimethoxy-5-methyl-6-(10'-hydroxydecyl)-1,4-benzoquinone (CV-2619) on adriamycin-induced ECG abnormalities and myocardial energy metabolism in spontaneously hypertensive rats]

Shimamoto N, Tanabe M, Hirata M

Nippon Yakurigaku Zasshi 1982 Oct;80(4):307-15

Antidote actions of CV-2619 and ubiquinone-10 (Q-10) against adriamycin (ADM) cardiotoxicity were studied in spontaneously hypertensive rats. ADM (1 mg/kg/day, i.p.) elicited widening of the QRS complex in the ECG. The widening of the QRS complex was counteracted by a 10-day treatment with CV-2619 (10 and 30 mg/kg/day, p.o.) or Q-10 (10 mg/kg/day, p.o.), which was started on the 15th day of the ADM treatment. CV-2619 or Q-10, however, did not influence ADM-induced decrease in body and heart ventricular weights. Systemic hypotension caused by adriamycin was accelerated by CV-2619 or Q-10. The ADM treatment significantly decreased myocardial glycogen and glucose contents, while it did not affect the lactate content. Furthermore, ADM did not affect the myocardial content of adenine nucleotides, but significantly increased that of creatine phosphate. CV-2619 or Q-10 medication did not counteract changes in these contents by ADM. On the contrary, both agents decreased the lactate content and increased the phosphorylation potential, an index of myocardial energy state. In conclusion, CV-2619 might be as effective as Q-10 to protect the heart against ADM cardiotoxicity, and both test agents improved the myocardial energy state.

Bioenergetics in clinical medicine. III. Inhibition of coenzyme Q10-enzymes by clinically used anti-hypertensive drugs.

Kishi H, Kishi T, Folkers K

Res Commun Chem Pathol Pharmacol 1975 Nov;12(3):533-40

Background data revealed that some American and Japanese patients with essential hypertension, including many who were not being treated with any anti-hypertensive drug, had a deficiency of coenzyme Q10. Eight clinically used anti-hypertensive drugs have now been tested for inhibition of two mitochondrial coenzyme Q10-enzymes of heart tissue, succinoxidase and NADH-oxidase. Diazoxide and propranolol significantly inhibited the CoQ10-succinoxidase and CoQ10-NADH-oxidase, respectively. Metoprolol did not inhibit succinoxidase, and was one-fourth as active as propranolol for inhibition of NADH-oxidase. Hydrochlorothiazide, hydralazine, and clonidine also inhibited CoQ10-NADH-oxidase. Reserpine did not inhibit either CoQ10-enzyme, and methyl dopa was a very weak inhibitor of succinoxidase. The internationally recognized clinical side-effects of propranolol may be due, in part, to inhibition of CoQ10-enzymes which are indispensable in the bioenergetics of cardiac function. A pre-existing deficiency of coenzyme Q10 in the myocardium of hypertensive patients could be augmented by subsequent treatment with propranolol, possibly to the "life-threatening" state described by others.

Bioenergetics in clinical medicine. Studies on coenzyme Q10 and essential hypertension.

Yamagami T, Shibata N, Folkers K

Res Commun Chem Pathol Pharmacol 1975 Jun;11(2):273-88

The specific activities (S.A.) of the succinate dehydrogenase-coenzyme Q10 (CoQ10) reductase of a control group of 65 Japanese adults and 59 patients having essential hypertension were determined. The mean S.A. of the hypertensive group was significantly

lower (p less than 0.001) and the mean % deficiency of enzyme activity was significantly higher (p less than 0.001) than the values for the control group. These data on Japanese in Osaka agree with data on Americans in Dallas. Some patients showed no CoQ10-deficiency, and others showed definite deficiencies. Emphasizing the CoQ10-enzyme for patient selection, CoQ10 was administered to hypertensive patients. Four individuals showed significant but partial reductions of blood pressure. Monitoring the CoQ10-enzyme before, during, and after administration of CoQ10 indicated responses. The maintenance of high blood pressure could be primarily due to contraction of the arterial wall. Contraction or relaxation of an arterial wall is dependent upon bioenergetics, which also provide the energy for biosynthesis of angiotensin II, renin, aldosterone, and the energy for sodium and potassium transport. A clinical benefit from administration of CoQ10 to patients with essential hypertension could be based upon correcting a deficiency in bioenergetics, and point to possible combination treatments with a form of CoQ and anti-hypertensive drugs.

[Prevention of cerebrovascular insults]

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Geriatrische Universitätsklinik, Kantonsspital Basel.
Schweiz Med Wochenschr 1994 Nov 12;124(45):1995-2004

Cerebrovascular infarction is the third leading cause of mortality following coronary heart disease and malignancies. WHO studies show that more than half of patients admitted for cerebrovascular infarction were not treated for hypertension. The risk factors for coronary heart disease and cerebrovascular infarction are not identical. Patients with systolic and diastolic hypertension, atrial fibrillation, stenosis of the carotid artery, and smoking, have a significantly elevated risk for cerebrovascular accidents. Hypercholesterolemia and diabetes are less important risk factors. Risk factors amendable by adequate nutritional intake are low supply of carotene and vitamin C. Homocysteineemia appears to be a risk factor that may be influenced by appropriate nutrition. Antihypertensive therapy is the most important primary and secondary preventive measure. No smoking and adequate dietary intake are also important. Primary prevention with low dose salicylic acid (ASA) is recommended in the presence of additional cardiovascular risk factors. The benefit of low dose anticoagulant therapy in atrial fibrillation without symptoms is not fully established. In subjects with atrial fibrillation with cerebrovascular events anticoagulants are superior to ASA. Surgical treatment of significant stenosis of the carotid artery is indicated. In secondary prevention of thromboembolic events, low dose ASA is recommended. A valuable alternative in case of side effects is available in ticlopidine.

[Essential antioxidants in cardiovascular diseases--lessons for Europe]

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Ther Umsch 1994 Jul;51(7):475-82

Complementary epidemiological studies consistently reveal a substantially increased risk of cardiovascular disease (CVD) at suboptimal plasma levels of essential antioxidants in comparison with optimum ranges of vitamin C (> 50 $\mu\text{mol/l}$), of lipid-standardized vitamin E (> 30 $\mu\text{mol/l}$ or a tocopherol/cholesterol ratio > 5.2 $\mu\text{mol/mmol}$), beta-carotene (> 0.4 $\mu\text{mol/l}$). The poor level of any single essential antioxidant can increase the risk, and the combination of suboptimal levels has additive or even overmultiplicative effects on the risk for CVD. Suboptimal antioxidant levels are stronger predictors of the severalfold regional differences of CVD in Europe than classical risk factor such as hypercholesterolemia, hypertension, etc. Scotsmen and Finns tend to suboptimal levels of essential antioxidants, whereas German-speaking regions may mostly reveal a fair vitamin E status, but at least one out of four subjects can reveal suboptimal levels of vitamin C and carotene, particularly in smokers. This deficit can be avoided by 'prudent diets' rich in fruits and vegetables as practiced by Frenchmen, Italians and Spaniards. The simultaneous correction of all suboptimal antioxidant levels appears to be a promising new means for CVD prevention, particularly in the northern parts of Europe. In the USA the risk of CVD could substantially be reduced without dietary modifications by voluntary daily supplements as follows: vitamin C > 140 mg, vitamin E > 100 IU (100 mg d,l- or 74 mg d-alpha-tocopherylacetate), and in current smokers by gamma-carotene > 8.6 mg. Hence, these antioxidants may be crucial constituents of diets rich in fruits and vegetables, which are by consensus associated with a lower risk of premature death from CVD (and cancer as well).

Antioxidant vitamin intake and coronary mortality in a longitudinal population study.

Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A
Social Insurance Institution, Helsinki, Finland.

Oxidation of lipoproteins is hypothesized to promote atherosclerosis and, thus, a high intake of antioxidant nutrients may protect against coronary heart disease. The relation between the intakes of dietary carotene, vitamin C, and vitamin E and the subsequent coronary mortality was studied in a cohort of 5,133 Finnish men and women aged 30-69 years and initially free from heart disease. Food consumption was estimated by the dietary history method covering the total habitual diet during the previous year. Altogether, 244 new fatal coronary heart disease cases occurred during a mean follow-up of 14 years beginning in 1966-1972. An inverse association was observed between dietary vitamin E intake and coronary mortality in both men and women with relative risks of 0.68 (p for trend = 0.01) and 0.35 (p for trend < 0.01), respectively, between the highest and lowest tertiles of the intake. Similar associations were observed for the dietary intake of vitamin C and carotenoids among women and for the intake of important food sources of these micronutrients, i.e., of vegetables and fruits, among both men and women. The associations were not attributable to confounding by major nondietary risk factors of coronary heart disease, i.e., age, smoking, serum cholesterol, hypertension, or relative weight. The results support the hypothesis that antioxidant vitamins protect against coronary heart disease, but it cannot be excluded that foods rich in these micronutrients also contain other constituents that provide the protection.

The decline in stroke mortality. An epidemiologic perspective.

Klag MJ, Whelton PK

Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.

Ann Epidemiol 1993 Sep;3(5):571-5

The evidence that treatment of hypertension prevents stroke is incontrovertible. Several observations, however, suggest that improvements in the prevalence of antihypertensive treatment cannot explain all of the recent decline in stroke mortality. Changes in nutritional patterns may explain some of the observed decline. Prospective studies have demonstrated conclusively an independent, increasing risk of hemorrhagic, but not thrombotic, stroke at higher levels of alcohol use. Stroke mortality is associated inversely with fat and protein intake. Dietary sodium has been linked to stroke in ecologic studies but not in prospective studies. Ecologic studies have suggested that foods high in vitamin C and potassium protect against stroke; an inverse association of potassium intake with fatal stroke has been demonstrated in cohort studies. Two studies in humans also suggest a protective effect of serum selenium against subsequent stroke. Determination of the influence of nutrients on stroke incidence offers tantalizing opportunities for future research and possibly, intervention.

Can antioxidants prevent ischemic heart disease?

Maxwell SR

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J Clin Pharm Ther 1993 Apr;18(2):85-95

Ischemic heart disease remains a major cause of mortality in developed countries. A number of important risk factors for the development of coronary atherosclerosis have been identified including hypertension, hypercholesterolaemia, insulin resistance and smoking. However, these factors can only partly explain variations in the incidence of ischaemic heart disease either between populations or within populations over time. In addition, population interventions based upon these factors have had little impact in the primary prevention of heart disease. Recent evidence suggests that one of the important mechanisms predisposing to the development of atherosclerosis is oxidation of the cholesterol-rich low-density lipoprotein particle. This modification accelerates its uptake into macrophages, thereby leading to the formation of the cholesterol-laden 'foam cell'. In vitro, low-density lipoprotein oxidation can be prevented by naturally occurring antioxidants such as vitamin C, vitamin E and beta-carotene. This article explores the evidence that these dietary anti-oxidants may influence the rate of progression of coronary atherosclerosis in vivo and discusses the need for formal clinical trials of antioxidant therapy.

Antioxidant therapy in the aging process.

Deucher GP

Clinica Guilherme Paulo Deucher, Sao Paulo, Brazil.

EXS 1992;62:428-37

A total of 1,265 patients with age-related diseases such as diabetes, arthritis, vascular disease and hypertension as well as 1,100 persons in diminished health without apparent disease, were treated with the metal chelator EDTA and antioxidants such as vitamin C, E, beta-carotene, selenium, zinc and chromium. Good results were observed in the majority of patients. This is encouraging for the initiation of controlled clinical trials.

Effect of flosequinan on ischaemia-induced arrhythmias and on ventricular cyclic nucleotide content in the anaesthetized rat.

Jones RB, Frodsham G, Dickinson K, Foster GA
Boots Pharmaceuticals, Research Department, Nottingham.
Br J Pharmacol (England) Apr 1993, 108 (4) p1111-6

1. Flosequinan, milrinone, isoprenaline and forskolin given intravenously at similarly hypotensive doses have been evaluated in separate studies for their effect on ischaemia-induced arrhythmias and on ventricular cyclic nucleotide content following coronary artery ligation in the pentobarbitone anaesthetized rat.
2. Flosequinan did not affect mortality or arrhythmias following coronary artery ligation in either study and no change in ventricular cyclic nucleotide content was observed.
3. Isoprenaline caused a significant increase in mortality ($P < 0.05$) in both studies whereas milrinone and forskolin caused a significant increase in mortality in only one of the two studies conducted. All three agents caused significant increases in cyclic AMP which were associated with increased incidence of arrhythmias.
4. When compared at similarly hypotensive doses, flosequinan, in contrast to milrinone, isoprenaline and forskolin, did not influence ischaemia-induced arrhythmias or raise ventricular cyclic nucleotide levels in the anesthetized rat.

What do the newer inotropic drugs have to offer?

Sasayama S
Second Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Japan.
Cardiovasc Drugs Ther 1992 Feb;6(1):15-8

Intensive interest and passion have been generated in the search for orally effective inotropes over the past few decades. Several extensive clinical evaluations of these agents have now been completed. Both beta- adrenergic agonists and phosphodiesterase inhibitors that exert cardiotoxic action by increasing intracellular cyclic adenosine monophosphate produced dramatic short-term therapy hemodynamic benefits in patients with advanced heart failure. However, patients who received long-term treatment with these agents had unfavorable outcomes, including a higher mortality and morbidity rate, and deleterious side effects. The principal mechanisms responsible for the limitations in its usefulness in long-term therapy may be related to increased energy expenditure and potential arrhythmogenic effects. In contrast to these pessimistic views, one quinolinone derivative has been shown to exert a positive inotropic action without a chronotropic effect. Patients with mild heart failure responded favorably to this agent in long- term therapy. The lack of an increase in heart rate might be the cause of this salutary effect. Concerns regarding the possible improvement in the prognosis of patients with heart failure due to the use of positive inotropic therapy still continue.

Arrhythmogenic effect of forskolin in the isolated perfused rat heart: Influence of nifedipine reduction of external calcium

Huang XD, Wong TM
Department of Physiology, Faculty of Medicine, University of Hong Kong.
Clin. Exp. Pharmacol. Physiol. (Australia), 1989, 16/10 (751-757)

This study investigated first the effects of forskolin on cardiac rhythm, and second the roles of calcium in cardiac arrhythmogenesis by cAMP. Two series of experiments were performed. In the first series, forskolin was administered into the isolated perfused rat heart. In the second series, forskolin administration was preceded by administration of nifedipine, a calcium channel blocker, or infusion of a low concentration calcium solution. In both experiments, the myocardial cAMP level and electrocardiogram were

determined. It was found that forskolin increased cAMP level as well as inducing arrhythmia. Pretreatment with nifedipine or a reduction of external calcium, that either maintained or further enhanced the forskolin-induced increase in the cAMP level, abolished the forskolin-induced arrhythmia. The results of the present study support the hypothesis that myocardial cAMP mediates cardiac arrhythmia, and provide evidence that calcium is essential in arrhythmia mediated by cAMP.

Hormone secretagogues increase cytosolic calcium by increasing cAMP in corticotropin-secreting cells

Luini A, Lewis D, Guild S, Corda D, Axelrod J
Proc. Natl Acad. Sci. U.S.A. (USA), 1985, 82/23 (8034-8038)

Corticotropin (ACTH)-releasing factor, vasoactive intestinal peptide, and catecholamines - hormones that stimulate ACTH secretion and cAMP generation - increased cytosolic calcium in AtT-20 cells. The increase in intracellular calcium is presumably a consequence of the stimulated cAMP synthesis, since forskolin, an activator of the catalytic unit of adenylate cyclase, and the cAMP analog 8-bromoadenosine 3',5'-cyclic monophosphate (8Br-cAMP) also increased the cytosolic levels of this ion. Pretreatment with somatostatin, a neuropeptide that inhibits stimulation of the adenylate cyclase system and the secretion of ACTH blocked the increase of cytosolic calcium. The effect of 8Br-cAMP, which bypasses the cyclase, was not inhibited by somatostatin pretreatment. The source of the increased calcium appears to be mainly extracellular. This is indicated by the inability of the secretagogues to increase cytosolic calcium in a medium deprived of this ion or in the presence of blockers of voltage-gated calcium channels. The involvement of calcium channels in the calcium rise evoked by the secretagogues was supported by experiments using the whole-cell patch-clamp technique. In these experiments 8Br-cAMP increased voltage-dependent calcium currents. These results suggest the following chain of events in the receptor-mediated elevation of cytosolic calcium and the concomitant release of ACTH from AtT-20 cells: hormone-receptor binding > or = cAMP synthesis > or = protein kinase activation > or = calcium channel activation > or = increase in cytosolic calcium > or = many steps > or = ACTH release. Phorbol myristate acetate, a compound which does not stimulate cAMP generation but enhances the release of ACTH in AtT-20 cells, decreased the cytosolic calcium level.

The genesis of arrhythmias during myocardial ischemia. Dissociation between changes in cyclic adenosine monophosphate and electrical instability in the rat

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It has been proposed that increases in tissue cyclic adenosine monophosphate during ischemia may be responsible for the induction of arrhythmias that occur during the early minutes of ischemia. We have tested this hypothesis using the isolated perfused rat heart with coronary artery occlusion for 30 minutes. In control hearts, after a transient small rise, cyclic adenosine monophosphate content remained close to its preischemic value (3.0 ± 0.1 nM/g dry weight) throughout the period of occlusion. Eight percent (1/12) of the hearts fibrillated. Ninety-two percent (11/12) of the hearts exhibited ventricular tachycardia, and the mean total number of premature ventricular complexes was 528 ± 121 . Inclusion of epinephrine (1.0 μ M) in the perfusion fluid elevated cyclic adenosine monophosphate prior to coronary occlusion (to 10.7 ± 0.6 nM/g dry weight) and also throughout the ischemic period. It also increased arrhythmias such that 83% (20/24) of hearts fibrillated, 100% exhibited ventricular tachycardia, and the mean number of premature ventricular complexes increased to 747 ± 86 . Inclusion of forskolin (0.2 μ M), which stimulates adenyl cyclase independently of the beta-receptor, increased cyclic adenosine monophosphate content to a greater extent than epinephrine, to 14.1 ± 0.9 nM/g dry weight before the onset of ischemia and to 8.2 ± 0.4 nM/g dry weight after 30 minutes of ischemia. Despite the large increases in cyclic adenosine monophosphate, there was no increase in rhythm disturbances which were less than those seen in controls. Thus, no hearts fibrillated, the incidence of ventricular tachycardia was reduced to 58% (7/12), and the mean number of premature ventricular complexes was greatly reduced (79 ± 29 , $P < 0.001$ compared to the number with drug carrier alone). Higher concentrations of both epinephrine and forskolin caused changes that were qualitatively similar to those seen with the lower concentrations. In addition, when hearts were paced at 400 impulses/min, again only epinephrine increased the severity of ischemia-induced arrhythmias. In conclusion, despite its ability to increase cyclic adenosine monophosphate content to a greater extent than epinephrine, forskolin exerts an antiarrhythmic effect. This suggests that increased cyclic adenosine monophosphate content is not necessarily involved in the genesis of ischemia-induced arrhythmias, and that some other facet of adrenoceptor stimulation or catecholamine action may be involved.

Effects of high K on relaxation produced by drugs in the guinea-pig tracheal muscle

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In the guinea-pig tracheal smooth muscle, effects of various relaxants were compared in normal (5.9 mM) and excess (40 mM) K media. The relaxing effect of calcium-channel blockers, nifedipine and verapamil (group I) was potentiated by increasing the external K concentration. The effect of the drugs which are supposed to increase intracellular cyclic AMP, such as isoprenaline, forskolin, isobutylmethylxanthine, theophylline, dibutyryl cyclic AMP (group II) was moderately reduced by excess K. Nitroprusside, 8-bromo-cyclic GMP and sodium nitrite (group III) are generally considered to increase intracellular cyclic GMP and their effect was markedly reduced by excess K. When the tension development was made the same at 5.9 mM K and 40 mM K by adjusting the Ca concentration, the relaxing effect was similar and independent of the K concentration both for group II and group III drugs. It seems that the group II drugs can better overcome a large influx of Ca than group III drugs.

Forskolin inhibits ouabain-sensitive ATPase in the medulla of rat kidney

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IRCS Medical Science (United Kingdom) 1983, 11/11 (957-958)

The diterpene forskolin, a cardiostimulant, vasodilatory and hypotensive drug, is a potent activator of adenylate cyclase but little is known about its effects on other membrane bound enzymes. Total ATPase, in the absence of ouabain, and ouabain-insensitive ATPase, in the presence of 1 mM ouabain, were measured by the enzymatic technique of Fritz and Hamrick. The difference between total and ouabain-insensitive ATPase activity is referred to as Na⁺K⁺-ATPase. The protein content was determined according to Lowry. In cortex homogenates, no significant modification of total, ouabain-insensitive and Na⁺K⁺-ATPase activities occurred in the presence of 10⁻⁶-10⁻⁴ M forskolin. In medulla homogenates, forskolin (10⁻⁶-10⁻⁴ M) caused a significant 55% decrease of Na⁺K⁺-ATPase activity. The inhibition is dose-dependent but not complete at 10⁻⁶-10⁻⁴ M forskolin, higher concentrations of the drug could, however, not be prepared because of its limited solubility. It would be interesting to correlate this result with a physiological difference of the cortical and medullary Na⁺K⁺-ATPase.

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