Alteration of Lipids, G Proteins, and PKC in Cell Membranes of Elderly Hypertensives

Pablo V. Escribá, José M. Sánchez-Dominguez, Regina Alemany, Javier S. Perona, Valentina Ruiz-Gutiérrez

Abstract—In this study, we quantified the levels of lipids and signaling proteins in erythrocyte membranes from elderly normotensive and hypertensive subjects. In hypertensive subjects, the cholesterol/phospholipid ratio increased significantly in erythrocyte membranes, owing to the reduction of phospholipid levels concomitant with a rise in the levels of cholesterol. In addition, differences were also found in the amount of fatty acids in both phospholipid and cholesterol esters. Erythrocyte membranes from hypertensive subjects contained higher levels of monounsaturated and lower levels of polyunsaturated fatty acids. On the other hand, signaling proteins such as G proteins and protein kinase C have been implicated in the control of blood pressure. Previous studies have shown that the cellular localization and the activity of these proteins are modulated by the type and the abundance of membrane lipids. For this reason, we assessed the levels of these signaling molecules in the membrane. We found that the levels of membrane-associated (active/preactive) G proteins (Gαi, Gαo, and Gβ) and protein kinase C were significantly reduced in hypertensive subjects. We believe that these alterations could be related to the etiopathology of hypertension in elderly subjects or alternatively may correspond to adaptive compensatory mechanisms. (Hypertension. 2003;41:176-182.)

Key Words: blood pressure ■ G proteins ■ elderly ■ protein kinases ■ membranes ■ lipids

Cardiovascular pathologies constitute the main cause of death in industrialized countries. Among the different manifestations and symptoms that arise during the development of cardiovascular illnesses, hypertension is a major risk factor, the control of which is one of the main aims of cardiovascular therapies. Multiple metabolic abnormalities accompany essential hypertension, and these include alterations in serum lipoprotein levels (HDL, LDL and VLDL), hypertriglyceridemia, hypercholesterolemia, insulin resistance, and so forth. In addition, alterations in the composition and properties of membranes have been reported both in hypertensive humans and animal models of hypertension. Modifications of membrane lipids change the physical and functional properties of the cell barrier, and such modifications could be reflected in alterations of cellular physiology in hypertensive subjects. Indeed, the cellular localization and activity of G proteins and protein kinase C (PKC) are modulated by membrane lipids and drugs that modulate the membrane structure.

G proteins and PKC are signaling elements critical in the propagation of messages from G-protein–coupled receptors (GPCRs). The relevance of G proteins and PKC in the control of blood pressure is reflected in the fact that a wide variety of GPCRs are involved in this physiological process. In this context, α1- and β-adrenoceptors have been shown to control blood pressure at different levels. The α1-adrenoceptor controls blood pressure centrally by activating Gi proteins, whose α-subunit inhibits the production of cAMP by adenyl cyclase. In contrast, α1- and β-adrenoceptors control blood pressure peripherally, activating phospholipase C and adenyl cyclase through Gαo and Gαq proteins, respectively. The effector proteins phospholipase C and adenyl cyclase regulate intracellular levels of second messengers, such as diacylglycerol, inositol phosphate, and cAMP. These second messengers, along with Gβγ-protein subunits, modulate the activity of other messengers, including various protein kinases (PKC, PKA, and GRK) that phosphorylate and modulate the activity of several proteins. Some of the targets of these kinases are activated GPCRs that, on phosphorylation, become desensitized.

In this scenario, alterations in membrane lipids and of signaling membrane proteins could be relevant to the pathophysiology of hypertension. On one hand, hypertension has been associated with multiple alterations in the physical properties of the plasma membrane. On the other hand, an impairment of the adrenoceptor/G protein/adenyl cyclase system has been consistently observed in hypertensive humans and animals, although the molecular basis of these alterations remains largely unknown.

This study was designed to evaluate the status of serum and membrane lipids as well as membrane-associated signaling proteins (G proteins and PKC) in erythrocytes of elderly hypertensive subjects.
normotensive and hypertensive subjects. Between these two groups, we found significant differences in the levels of membrane lipids, G proteins, and PKC. In erythrocytes from hypertensive subjects, an increase in the levels of membrane cholesterol and a decrease in total phospholipids was found, as were alterations in the relative abundance of their fatty acid moieties. Immunochemical quantification of membrane-bound G proteins revealed decreases in different G-protein subunits. Finally, the amount of PKCα was significantly lower in hypertensive subjects with respect to normotensive subjects.

In summary, this work presents relevant data that could explain the alterations of GPCR signaling associated with hypertension in elderly (and possibly other) subjects. It is likely that alterations in membrane lipid levels in hypertensive subjects affected the localization and activity of G proteins, PKC, and possibly other signaling proteins. These changes could explain the observed impairment in signal propagation from GPCRs in hypertensive subjects.

Methods

Subjects

Elderly hypertensive and normotensive (control) subjects were studied. The hypertensive and control groups each consisted of 28 subjects (Table 1). Blood pressure was measured with a mercury-gauge sphygmomanometer on the right brachial artery of each subject. At each visit, 3 blood pressure readings were recorded, and the average was used to determine the eligibility of the subject. In addition, the subject’s blood pressure was recorded at the beginning and end of each period of study. The criterion for hypertension was a systolic blood pressure ≥140 mm Hg and a diastolic value of ≥90 mm Hg on at least 3 different occasions. Blood pressure was recorded after the subject had been at rest in a supine position for 10 minutes. Before recruitment, the medical histories of all the participants were reviewed comprehensively, and a physical examination and clinical chemical analysis were performed to exclude possible secondary causes of hypertension. None of the subjects used in the study had diabetes mellitus or hypothyroidism, and no history of alcohol abuse or cigarette smoking was seen. All subjects gave their informed consent before participating in the study. Hypertensive subjects were treated with enalapril, felodipine, spironolactone, or amlodipine, but none of these drugs has been reported to alter the levels of the proteins studied here. Biochemical and physiological parameters indicated that the control group was healthy. All the protocols used in this study were approved by the Institutional Committee of Human Research (Comité de Ensayos Clínicos, Hospital Universitario Virgen del Rocío, Sevilla, Spain).

Biochemical and Plasma Lipid Measurements

Levels of blood glucose, creatinine, and uric acid were measured by conventional enzymatic methods, with the use of venous blood obtained on the day of the examination after overnight fasting. Similarly, LDL, HDL, and total cholesterol, phospholipids, and triglycerides in serum were measured by enzymatic methods.31,32

Preparation of Erythrocytes

Erythrocyte membranes were prepared as described previously.4–8 Briefly, blood samples obtained after overnight fasting were collected in heparinized tubes and centrifuged at 1750g at 4°C for 10 minutes. The plasma and buffy coat were removed, and the erythrocyte pellet was washed twice with 110 mmol/L MgCl₂. Aliquots of this preparation were used to simultaneously determine the membrane lipid and protein content.

Analysis of Lipid Classes and Fatty Acid Methyl Esters

Quantitative extraction of total erythrocyte membrane lipids from 5 mL of blood was carried out as described elsewhere.33–35 Lipid extracts were dissolved in chloroform/methanol (2:1 vol/vol) and passed through 0.2-μm filters. They were then analyzed by liquid chromatography, as described previously, with the use of standard solutions for both identification and quantification.4–11 Lipids were also separated by thin-layer chromatography on silica gel plates (Kieselgel 60 F254, Merck). The mobile phase was a mixture of hexane/diethyl ether/acetic acid (80:20:1 vol/vol/vol), as described.96 The phospholipid and cholesteryl-ester fractions were transmethylated, and the resulting fatty acid methyl esters were analyzed by gas chromatography.96 Individual fatty acid methyl esters were identified by comparison with known standards or by gas chromatography–mass spectrometry.

Immunoblot Analysis and Quantification of G Proteins and PKCα

Immunoblotting of G proteins and PKCα from erythrocyte membranes of elderly normotensive (control) or hypertensive subjects was performed as described elsewhere.37–39 Briefly, a pellet of erythrocytes from 1 mL of blood was combined with 1 mL of homogenization buffer (50 mmol/L Tris–HCl [pH 7.5], 1 mmol/L EDTA, 2 mmol/L MgCl₂, 1 mmol/L PMSF, and 5 mmol/L iodoacetamide) and homogenized with a blade-type homogenizer. The samples were then centrifuged at 600g and 4°C for 5 minutes. The pellets that contained whole cells were discarded, and the supernatants were then centrifuged twice at 40,000g and 4°C for 20 minutes. These final pellets contained the erythrocyte membranes, and they were resuspended in 500 μL of homogenization buffer and 250 μL of solubilization buffer (160 mmol/L Tris–HCl [pH 6.8], 8% sodium dodecyl sulfate). The protein content of these samples was then determined by means of the bicinchoninic acid method.98 Finally, the sample proteins were separated by electrophoresis and immunoblotted with the following specific primary antibodies, as described elsewhere:37–52 anti-Gα12 (1:7000 dilution), anti-Gα13 (1:5000; used to measure the 52-kDa band),37–39 anti-Gαo (1:4000), and anti-Gβ (1:5000) were from New England Nuclear Corp, and anti-PKCα (1:1000) was from BD Transduction Laboratories. The primary antibodies were detected with horseradish peroxidase–linked secondary antibodies (1:2000 dilution; Amersham Pharmacia) and visualized with the enhanced chemiluminescence Western blot detection system (Amersham Pharmacia) exposed to enhanced chemiluminescence hyperfilm (Amersham Pharmacia). Quantification was performed by image analysis as described.37

### Table 1. Characteristics of Hypertensive and Control Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hypertensive Subjects</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>83±1</td>
<td>86±1</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>7/21</td>
<td>6/22</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.1±1.1</td>
<td>28.1±0.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76.6±1.9</td>
<td>72.4±2.1‡</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>145.2±4.2</td>
<td>140.4±4.0‡</td>
</tr>
<tr>
<td>Total serum cholesterol, mg/dL</td>
<td>184.8±7.7</td>
<td>185.7±7.3</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dL</td>
<td>114.2±5.5</td>
<td>113.4±6.6</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dL</td>
<td>51.7±3.2</td>
<td>56.6±3.9§</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>94.6±6.4</td>
<td>77.8±5.3†</td>
</tr>
<tr>
<td>Phospholipids, mg/dL</td>
<td>178.5±7.1</td>
<td>182.0±4.8*</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM. LDL indicates low-density lipoproteins in serum; HDL, high-density lipoproteins in serum. *P<0.05, †P<0.01, ‡P<0.001 vs hypertensive subjects.
Statistical Analysis

The results of the statistical analyses are expressed as mean±SEM. One-way ANOVA, followed by the Scheffé test, was used for statistical evaluations. Differences between experimental groups were considered statistically significant at a value of \( P<0.05 \).

**Results**

The demographic characteristics, blood pressure, and serum lipid/lipoprotein levels of the subjects used in this study are shown in Table 1. The mean±SEM levels of glucose, creatinine, and uric acid in control subjects were 101±3 mg/dL, 0.97±0.18 mg/dL, and 4.9±1.4 mg/dL, respectively. In hypertensive subjects (\( n=28 \)), these values were 95±13 mg/dL, 1.1±0.24 mg/dL, and 5.5±1.5 mg/dL, respectively. In the control group, mean±SEM blood pressure was 140±4.0 mm Hg (\( n=28 \)), a normal value for subjects of this age (86±1 years). The hypertensive group had a significantly higher systolic blood pressure value (145.2±4.2 mm Hg, \( P<0.001 \), \( n=28 \)) (Table 1). Diastolic blood pressure was also significantly higher in elderly hypertensive subjects (72.4±2.1 mm Hg and 76.6±2.2 mm Hg for normotensives and hypertensives, respectively; \( P<0.001 \)) (Table 1).

**Serum Lipoproteins in Elderly Hypertensive Subjects**

Although no significant differences in total cholesterol were observed, a significant decrease in the levels of HDL-cholesterol was found in elderly hypertensives (56.8±3.5 mg/dL and 51.7±3.2 mg/dL in normotensive and hypertensive subjects, respectively, \( P<0.001 \)) (Table 1). Increased levels of serum triglycerides were also found in this group (77.8±5.3 mg/dL and 94.6±6.4 mg/dL for normotensive and hypertensive subjects, respectively; \( P<0.01 \)). In contrast, the hypertensive group had lower levels of phospholipids (182±5 mg/dL and 178±7 mg/dL in normotensives and hypertensives, respectively, \( P<0.05 \)) (Table 1). These alterations are characteristic features of hypertensive subjects, further evidence of their pathological status.\(^4\)-\(^8\)

**Erythrocyte Membrane Lipids in Elderly Hypertensive Subjects**

Erythrocyte membranes from elderly hypertensive subjects contained a higher percentage of cholesterol with respect to the total lipid content in normotensive and hypertensive subjects, respectively (23.5±1.5% and 25.8±0.9%; \( P<0.05 \); Table 2). In contrast, the percentage of phospholipids was lower in hypertensive subjects than in control subjects (63.6±1.5% and 59.9±1.9% in control and hypertensive subjects, respectively, \( P<0.05 \)) (Table 2). These changes resulted in a marked and significant \( (P<0.05) \) increase of the cholesterol/phospholipid ratio in hypertensive subjects (0.37±0.1 and 0.44±0.0 in normotensive and hypertensive subjects, respectively, \( P<0.05 \)).

Differences were also found in the levels of the fatty acid moieties of phospholipids and cholesterol esters from erythrocyte membranes. Apart from particular changes in the levels of distinct fatty acid species, monounsaturated fatty acids were more abundant in hypertensive subjects, whereas, the content of polyunsaturated fatty acids was higher in blood cell membranes from control subjects (Table 3).

**Density of G-Protein Subunits and PKCα in the Erythrocyte Membranes of Elderly Hypertensive Subjects**

The precise quantification of membrane proteins in normotensive and hypertensive subjects was achieved through quantitative immunoblotting. The correlation between the amount of protein loaded on the gel and integrated optical density (IOD) values was linear in the ranges used. In addition, the steep slope of the curve ensured the reliability of the data. These analyses showed that pertussis toxin–sensitive G-protein \( \alpha \)-subunit levels were reduced in blood cell membranes of hypertensive subjects. Specifically, the levels of the adenyl cyclase inhibitory G-protein \( \alpha \)-subunit, \( \alpha \)-subunit, \( \alpha \)-subunit, \( \alpha \)-subunit, and \( \beta \)-subunit, the levels of \( \alpha \)-proteins were significantly and markedly reduced in the hypertensive group (decreases of 38±11%, \( P<0.01 \); Figure 1). Similarly, the levels of \( \alpha \)-proteins were significantly and markedly reduced in the hypertensive group (decreases of 38±11%, \( P<0.01 \); Figure 1). However, the decrease observed in the levels of choleratoxin–sensitive G protein (52-kDa \( \alpha \)-protein) was not statistically significant in hypertensive subjects (decreases of 16±7%, \( P>0.05 \), Figure 1). With respect to the common G-protein \( \beta \)-subunit, the levels of this protein were also downregulated in blood cells of elderly hypertensive patients (decreases of 21±8%, \( P>0.05 \), Figure 2). Finally, the levels of PKCα also showed a marked and significant decrease in the membranes of red blood cells from elderly hypertensive subjects (decreases of 32±8%, \( P<0.01 \), Figure 2).

**Discussion**

Cells exert an exquisite control of lipid levels both in plasma and organelle membranes.\(^40\) The characteristic properties of membranes are dictated by the specific combinations of membrane lipids and proteins that they contain. In this context, the changes in membrane lipid and protein levels in erythrocyte membranes reported here are most probably associated with alterations in cell behavior in elderly hypertensive subjects. These results are of special relevance to the field of cell signaling because a direct relation between membrane lipid levels in human erythrocytes and neurons has been recently discovered.\(^41\) Therefore, the changes found in blood cells could reflect alterations in other cell types that control blood pressure.
Different properties of the membrane lipid fraction modulate the activity of membrane proteins. In this context, it has been demonstrated that the membrane cholesterol content (also defined by the cholesterol/phospholipid ratio) regulates the membrane fluidity or microviscosity. Thus, an increase in this ratio is associated with a decrease in membrane fluidity. In addition to cholesterol, the type and abundance of fatty acids (free or esterified) also contribute to the modulation of membrane fluidity. We found that erythrocyte membranes from hypertensives have a higher cholesterol content (also defined by the cholesterol/phospholipid ratio) than those from normotensive subjects (0.37 ± 0.1). This result is in agreement with previous studies showing that the hydrophobic core of erythrocyte membranes is less fluid in hypertensive rats. Moreover, we found differences in the fatty acid composition of erythrocyte membranes that may further alter the plasma membrane fluidity in hypertensive subjects. Also, in line with these results, vascular cells of spontaneously hypertensive rats exhibit differences in membrane fatty acids that may contribute to a lower membrane fluidity.

Previous studies have also associated hypertension with multiple plasma membrane alterations. Since membrane fluidity regulates the activity of several membrane proteins, the lipid alterations observed in membranes of elderly hypertensive subjects could be involved in altering membrane protein function. Membrane lipids also regulate the formation of hexagonal (HII) phases, nonlamellar membrane structures that organize into tubular micelles. HII phases are critical in cells, where they influence the localization and activity of membrane proteins, G proteins and PKC are signaling molecules capable of translocating from the cytosol to membranes. They propagate and amplify messages from membrane GPCRs (eg, those which control the blood pressure) to other signaling proteins, and their localization is modulated by the membrane lipid composition and HII-phase propensity. In the knockouts of the α2- and β12-adrenoceptors, it has been shown that these receptor types are implicated in the central and peripheral control of blood pressure, respectively. These receptors use Gαi, Gαo, and Gαs proteins, further evidence that the results presented here are associated with the control of blood pressure. The levels of Gαi2 and Gαo were seen here to be markedly and significantly lower in erythrocyte membranes from hypertensive subjects (decreases of 31 ± 10% and 38 ± 11% for Gαi and Gαo, respectively, P < 0.01), possibly as the result of membrane lipid alterations. Although the common Gββ-subunit also appeared to be reduced in hypertensive subjects (21 ± 8% decreases, P < 0.05), Gα levels

### Table 3. Fatty Acid Composition of Phospholipids and Cholesterol Esters in Erythrocytes Membranes (mg/100 mg)

<table>
<thead>
<tr>
<th>Fatty Acid Species</th>
<th>Phospholipids</th>
<th>Cholesterol Esters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypertensives</td>
<td>Controls</td>
</tr>
<tr>
<td>C14:0</td>
<td>0.4 ± 0.1</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>C14:1-5</td>
<td>1.7 ± 0.2</td>
<td>2.2 ± 0.3†</td>
</tr>
<tr>
<td>C16:0</td>
<td>23.7 ± 0.6</td>
<td>23.1 ± 0.5</td>
</tr>
<tr>
<td>C16:1-9</td>
<td>0.4 ± 0.0</td>
<td>0.3 ± 0.0</td>
</tr>
<tr>
<td>C16:1-7</td>
<td>0.5 ± 0.0</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>C16:4n-3</td>
<td>2.6 ± 0.3</td>
<td>2.5 ± 0.5</td>
</tr>
<tr>
<td>C18:0</td>
<td>16.6 ± 0.3</td>
<td>17.1 ± 0.6</td>
</tr>
<tr>
<td>C18:1n-9</td>
<td>0.9 ± 0.1</td>
<td>0.6 ± 0.0‡</td>
</tr>
<tr>
<td>C18:1n-9</td>
<td>16.3 ± 0.6</td>
<td>16.0 ± 0.8</td>
</tr>
<tr>
<td>C18:1n-7</td>
<td>1.8 ± 0.1</td>
<td>2.0 ± 0.2†</td>
</tr>
<tr>
<td>C18:2n-6</td>
<td>12.5 ± 0.7</td>
<td>13.4 ± 0.7*</td>
</tr>
<tr>
<td>C18:3n-6</td>
<td>0.4 ± 0.0</td>
<td>n.d.‡</td>
</tr>
<tr>
<td>C18:3n-3</td>
<td>0.3 ± 0.0</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>C20:2n-6</td>
<td>2.1 ± 0.1</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>C20:4n-6</td>
<td>17.0 ± 0.4</td>
<td>16.5 ± 0.4</td>
</tr>
<tr>
<td>C22:4n-6</td>
<td>0.7 ± 0.3</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>C22:6n-3</td>
<td>0.7 ± 0.1</td>
<td>0.8 ± 0.2</td>
</tr>
<tr>
<td>C24:1n-9</td>
<td>1.5 ± 0.1</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td>Total SFA</td>
<td>41.2 ± 1.1</td>
<td>41.1 ± 0.7</td>
</tr>
<tr>
<td>Total MUFA</td>
<td>22.6 ± 0.6</td>
<td>21.7 ± 0.7*</td>
</tr>
<tr>
<td>Total PUFA</td>
<td>36.2 ± 1.2</td>
<td>38.2 ± 0.9†</td>
</tr>
<tr>
<td>PUFA:SFA</td>
<td>0.8 ± 0.04</td>
<td>0.9 ± 0.03</td>
</tr>
<tr>
<td>PUFA:MUFA</td>
<td>1.6 ± 0.1</td>
<td>1.7 ± 0.1</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM (n = 28). SFA indicates saturated fatty acids; MUFA, monounsaturated fatty acids; and PUFA, polyunsaturated fatty acids.

*P < 0.05, †P < 0.01, ‡P < 0.001 vs hypertensives; n.d., not detected.
were not significantly decreased in hypertensive subjects (16±7%, P>0.05). These alterations in the levels of membrane G proteins could be associated with the reduced G-protein function and/or decreased receptor–G protein coupling described elsewhere, which may alter vasodilator function in hypertensive subjects.25

A reduction in G-protein activity in blood cells of older and hypertensive subjects has been reported previously.29 Although these changes were not accompanied by modulations in whole-cell G-protein levels, they may possibly have been associated with the decreases in membrane G proteins described here. Our study was carried out in cell membranes, so that the levels of G proteins found corresponded to active and/or preactive signal transduction components and may account for alterations in signal propagation. In line with this study and previous works, it has been observed that high blood pressure is associated with downregulation or loss of responsiveness of α-adrenoceptors in elderly hypertensive subjects.54

PKC was also found to be reduced in the membranes isolated from hypertensive subjects. As for G proteins, the cellular localization of this signaling enzyme is modulated by the membrane lipid composition and H₂-phase propensity.15,48 This enzyme is a key element in many GPCR-related signals, including the control of blood pressure.55 Adrenoceptors (and other GPCRs) can activate PKC through phospholipase C–induced diacylglycerol production. Activated PKC translocates to the plasma membrane,56 where it phosphorylates the serine/threonine residues of a wide variety of proteins, including adrenoceptors and other GPCRs.20,21,57–59 The half-life of activated PKC is less than 1 hour, as the result of its degradation by proteases.60 Therefore, lower PKC levels could either be the result of decreased mRNA expression or increased enzyme activation (and subsequent degradation). The former possibility would be parallel to a decrease in receptor phosphorylation, whereas the latter would be associated with increased receptor phosphorylation and desensitization. Various facts favor the latter hypothesis. First, it has been shown that PKC activation is followed by its degradation, so that protein levels appear to be reduced despite of an elevation in mRNA expression.61,62 Second, an increase in PKC activation would result in increased receptor phosphorylation and reduced adrenoceptor-associated signaling.63 Third, a greater degree of receptor desensitization coupled with lower G-protein levels is in agreement with previous studies demonstrating impaired adrenoceptor signaling. However, this matter requires further investigation because the relevance of this protein in the control of blood pressure and atherosclerosis has also been associated with other signaling events, such as the regulation of endothelin-1, the cytosolic levels of Ca²⁺, and so forth.63,64 Moreover, it is possible that PKC may exert different or even opposite effects in central and peripheral systems.

In summary, we have found alterations in the levels of erythrocyte membrane lipids in elderly hypertensive subjects that could account for the alterations in the levels of membrane-associated G proteins and PKC also observed here. The decreases in G protein and PKC levels in erythrocyte membranes probably alters GPCR-related signaling in these hypertensive subjects. GPCR-associated signaling alterations could be involved in the etiopathology of hypertension in elderly subjects or may constitute an adaptive mechanism in response to other alterations.
Perspectives

In industrialized countries, cardiovascular pathologies are involved in about one half of all deaths. In fact, if we want to live longer and healthier, it is essential to control cardiovascular, tumoral, and neurodegenerative risk factors. In increasingly aging societies, the knowledge of the molecular alterations underlying high blood pressure in elderly hypertensive subjects and its control are crucial issues. In this study, we highlight some molecular alterations associated with hypertension in elderly subjects. We found that the levels of certain membrane lipids are altered in elderly hypertensive subjects. Specifically, we have shown that the cholesterol/phospholipid ratio and the levels of monounsaturated fatty acids were higher in this group compared with normotensive control subjects, who in turn had lower levels of polyunsaturated fatty acids. We have previously demonstrated that the levels and the types of membrane lipids modulate membrane structure and regulate G protein–membrane and PKC-membrane interactions. When we studied the membrane levels of these proteins, we found significant and marked changes in elderly subjects with high blood pressure. It is feasible that the changes we found in signaling proteins in the membrane were related to alterations in the protein-lipid interactions that resulted from the altered lipid levels. If this hypothesis is correct, it may also be possible to control high blood pressure by modulating the membrane lipid structure. In this context, we have developed molecules capable of acting in this manner, and we have called this therapeutic approach “lipid therapy.” We believe that such an approach will become more widespread during the next decades and hence provide many benefits to human health.

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References


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