Na\(^+\) and K\(^+\) Transport Damage Induced by Oxygen Free Radicals in Human Red Cell Membranes

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The treatment of human erythrocytes with phenazine methosulfate (PMS) results in a sustained intracellular production of oxygen free radicals as shown by the reduction of nitroblue tetrazolium and methemoglobin production. Inhibition of superoxide dismutase by diethyldithiocarbamate further enhances nitroblue tetrazolium reduction indicating an increase in the PMS-dependent oxygen free radicals. NADH is one of the hydrogen donors able to react with oxygen free radicals in cyclic reactions which last far more than 4 h.

The attack of red cell membranes by oxygen free radicals greatly alters their chemical structure. We observed lipid peroxidation, as shown by the increase in malondialdehyde above endogenous levels and hemoglobin binding to the cell membrane.

PMS treatment markedly modifies the ionic equilibrium of the erythrocytes. At low PMS concentrations they lose intracellular K\(^+\). This is a prehemolytic effect, since hemolysis occur at high PMS concentrations. Both toxic effects are enhanced by superoxide dismutase inhibition with diethyldithiocarbamate, strongly suggesting that they result from the attack of cell membranes by oxygen free radicals. A study of the effect of PMS on the different transport pathways for K\(^+\) across the human red cell membrane showed that at low PMS concentrations there is a specific increase in passive K\(^+\) permeability with no major effect on the specific K\(^+\)-carriers such as the (Na\(^+\),K\(^+\))-pump or the (Na\(^+\),K\(^+\))-cotransport system. The increase in passive K\(^+\) permeability has the following properties: (i) it is not affected by ethylene glycol bis(β-aminoethyl ether)N,N,N',N'-tetraacetic acid, quinoline, or the replacement of Cl\(^-\) by NO\(_3\)\(^-\); (ii) it is enhanced by inhibition of the anion carrier with 4,4'-diisothiocyanato-2,2'-disulfonic acid stilbene; (iii) it is partially inhibited by external superoxide dismutase; and (iv) it is not affected by external catalase or by inhibition of endogenous catalase with 3-amino-1,2,4-triazole.

Our results strongly suggest that the PMS-dependent erythrocyte K\(^+\) loss results from membrane lipid peroxidation by oxygen free radicals, particularly O\(_2^\cdot\).
endogenous superoxide dismutase of intact red cells. The addition of 1 mM DDC to a medium containing 5 units/ml of purified superoxide dismutase and PMS-NADH-NBT is sufficient to inhibit 100% of the superoxide dismutase activity. Moreover, the incubation of intact human red cells with 1 mM DDC for 30 min at 37 °C inhibits 78 ± 10% of initial superoxide dismutase activity (mean ± range of three healthy donors). Superoxide dismutase activity was measured using the procedure of Winterbourn et al. (41).

Measurement of Intracellular NADH in Human Erythrocytes—Washed red cells were suspended in cold (Na⁺,K⁺)-Ringer medium (in which glucose was replaced by 10 mM deoxy glucose) with different concentrations of PMS. The final hematocrit was about 10%. Tripli-cate plastic tubes were incubated for 4 h at 37 °C. To stop the reaction, tubes were transferred to 4 °C for 1 min. The red cell pellet was washed twice with isosmotic NaCl and then hemolyzed with distilled water to a final volume of 2.5 ml. 0.25 ml of 10 N NaOH was added to the hemolysates, which were immediately vortexed. 0.275 ml of 30% phosphoric acid was then added and the tubes vortexed for a second time. Each procedure of protein precipitation with NaOH and H₂PO₄ was carried out in less than 1 min. This extremely exothermic reaction is probably responsible for the protein precipitation. We developed this procedure of protein precipitation because the classical methods (trichloroacetic acid, heat, etc.) were unable to preserve NADH content. NADH was measured in the supernatant by fluorimetry (excitation, 366 nm; emission, 455 nm) (34). The calibration curve has been obtained by measuring the content of different NADH concentrations exposed under the same conditions to NaOH and H₂PO₄. This calibration curve is comparable to one obtained in H₂O.

Malondialdehyde Measurement—Washed red cells were diluted in a cold Mg²⁺, sucrose medium. The red cell pellet was washed twice with isosmotic NaCl and then hemolyzed with distilled water to a final volume of 2.5 ml. 0.25 ml of 10 N NaOH was added, and the tubes were vortexed. 0.21 ml of 30% phosphoric acid was then added, and the tubes were vortexed for a second time. Each procedure of protein precipitation with NaOH and H₂PO₄ was carried out in less than 1 min. This extremely exothermic reaction is probably responsible for the protein precipitation. We developed this procedure of protein precipitation because the classical methods (trichloroacetic acid, heat, etc.) were unable to preserve NADH content. NADH was measured in the supernatant by fluorimetry (excitation, 366 nm; emission, 455 nm) (34). The calibration curve has been obtained by measuring the content of different NADH concentrations exposed under the same conditions to NaOH and H₂PO₄. This calibration curve is comparable to one obtained in H₂O.

Methemoglobin Measurement—The MetHb content of PMS-treated human red cells was measured using the above protocol. In 6 different experiments, we observed that reduced MetHb appears immediately after PMS incubation and increases linearly in time for at least 3–5 h, suggesting that PMS reacts with intracellular hydrogen donors to generate oxygen free radicals (19). Such a generation of free radicals can be followed spectrophotometrically by the reduction of NBT. In recent experiments we observed that PMS-like compounds may easily enter erythrocytes. Thus, we decided to see whether oxygen free radicals may be generated directly in red human cells by incubation with PMS.

Fig. 1 shows that in PMS-treated erythrocytes, there is a net increase in the reduced form of NBT above control levels. In 6 different experiments, we observed that reduced MetHb appears immediately after PMS incubation and increases linearly in time for at least 3–5 h, suggesting that PMS reacts with intracellular hydrogen donors to generate oxygen free radicals (Fig. 1). Further support of this mechanism came from the fact that when the erythrocyte superoxide dismutase is inhibited by DDC, there is an increase in reduced NBT (Fig. 1).

In control experiments, we observed that PMS is only able to transform hemoglobin into MetHb if NADH is present in the medium (see also Ref. 22). This indicates that this reaction is mediated by the oxygen free radicals generated by the reaction between PMS, NADH, and O₂ (19). In PMS-treated erythrocytes, there is a marked and rapid MetHb production (Fig. 2, A and B) further suggesting the generation of intracellular oxygen free radicals.

The Effect of PMS on the Intracellular NADH Content of Human Red Cells—It is thought that one of the intracellular substrates capable of reacting with PMS to generate oxygen free radicals is NADH. One experimental problem in demonstrating a reaction between PMS and NADH is that this latter is regenerated by glycolysis.

3 R. P. Garay, unpublished results.
Thus, we measured the intracellular content of NADH after PMS treatment in erythrocytes in which glycolysis was inhibited by the addition of deoxyglucose (Table I). Under these conditions, we were able to show a 20–30% decrease in NADH content after 4 h of incubation with PMS.

Lipid Peroxidation in PMS-treated Erythrocytes—It is now well established that oxygen free radicals are able to peroxidate unsaturated phospholipids of different membrane preparations (24, 25). This phenomenon is currently studied by measuring one of the products of this reaction: MDA. Table II shows that in ghosts prepared from PMS-treated erythrocytes, there is an increase in MDA content above endogenous levels which is further increased by the inhibition of superoxide dismutase by DDC.

MetHb-binding to the Red Cell Membrane—A small fraction of the formed MetHb in PMS-treated erythrocytes remains firmly bound to the red cell membrane (Table III). The amount of bound MetHb is further increased by inhibition of superoxide dismutase with DDC, suggesting a reaction between MetHb and some product of the reaction between the membrane and the oxygen free radicals.

The Effect of PMS on the Intracellular Na⁺ and K⁺ Content of Human Erythrocytes—The addition of PMS to human erythrocytes incubated in physiological (Na⁺,K⁺)-Ringer medium induces a loss of cell K⁺ which is accompanied by a less important gain in intracellular Na⁺. This phenomenon is enhanced by the inhibition of superoxide dismutase by DDC (Fig. 3A and B).

The Effect of PMS on the Erythrocyte (Na⁺,K⁺)-pump—Ouabain-sensitive Na⁺ efflux was measured in fresh human erythrocytes treated with different concentrations of PMS. Fig. 4 shows that the (Na⁺,K⁺)-pump is resistant to PMS treatment because high PMS concentrations are required to inhibit the (Na⁺,K⁺)-pump. In 8 healthy donors, the PMS concentration for half-maximal pump inhibition varied from 0.8 to 3 mM (mean: 1.1 mM) (Fig. 10).

Fig. 5 shows that the molecular mechanism of action of PMS involves inhibition of the maximal rate of the (Na⁺,K⁺)-pump without any observable effect on the apparent affinity for intracellular Na⁺.

The Effect of PMS on the Erythrocyte (Na⁺,K⁺)-Cotransport System—Bumetanide-sensitive Na⁺-efflux was measured in fresh human erythrocytes treated with different concentrations of PMS (Fig. 4). We observed that the (Na⁺,K⁺)-cotransport system could be inhibited by high PMS concentrations lower than those used for inhibiting the (Na⁺,K⁺)-pump. In 6 healthy donors, the PMS concentration for half-maximal inhibition varied from 0.1 to 0.5 mM (mean: 0.33 mM) (Fig. 10).

Fig. 6 shows that the molecular mechanism of PMS action on this cotransport system is similar to that on the (Na⁺,K⁺)-pump, i.e. inhibition of the maximal rate without affecting the apparent affinity for intracellular Na⁺.

The Effect of PMS on the Passive K⁺ and Na⁺ Permeabilities—Passive K⁺ permeability, but not passive Na⁺ permeability, increases with very low doses of PMS (Fig. 4). Indeed, Fig. 10 shows that in 24 healthy donors, the passive K⁺ permeability is stimulated by PMS concentrations as low as 0.01 to 0.03 mM. This is the transport parameter most affected by PMS.

Fig. 7 shows that the PMS-dependent increase in passive K⁺ permeability is linear with the increase in intracellular K⁺.

### Table I

| PMS Concentration (mM) | Subject 1 | Subject 2 | Subject 3 |
|------------------------|-----------|-----------|-----------|
| 0                      | 56.0 ± 1.9| 59.6 ± 3.5| 70.0 ± 1.3|
| 0.5                    | 44.6 ± 2.6| 46.5 ± 1.8| 48.3 ± 0.6|
| 1.0                    | 46.9 ± 1.8| 53.3 ± 3.1|           |
| 2.0                    | 49.6 ± 2.7| 54.4 ± 0.9|           |

### Table II

| Conditions | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 |
|------------|-----------|-----------|-----------|-----------|-----------|
|            | µM/liter of cells | µM/liter of cells | µM/liter of cells | µM/liter of cells | µM/liter of cells |
| Control    | 7.6 ± 0.6  | 9.7 ± 0.6  | 9.5 ± 0.8  | 8.1 ± 1.9  | 5.7 ± 0.4  |
| 2 mM PMS   | 13.5 ± 0.9 | 16.0 ± 0.9 | 13.4 ± 1.2 | 14.0 ± 1.7 | 6.2 ± 0.1  |
| 2 mM PMS + | 17.4 ± 0.9 | 21.4 ± 0.5 | 16.3 ± 1.8 | 18.7 ± 1.8 | 10.8 ± 1.1 |
TABLE III
The effect of oxygen free radicals on MetHb binding to human red cell membranes

Values are given as mean ± range of triplicate. A similar result has been obtained in three other experiments.

| Conditions          | Bound MetHb µM/liter of cells | % total Hb |
|---------------------|-------------------------------|------------|
| Control             | 215 ± 2                       | 4.3 ± 0.4  |
| 2 mM PMS            | 355 ± 1.5                     | 7.1 ± 0.3  |
| 2 mM PMS + 1 mM DDC |                               |            |

A similar result has been obtained in three other experiments.

Conditions Bound MetHb µM/liter of cells % total Hb
Control 215 ± 2 4.3 ± 0.4
2 mM PMS 355 ± 1.5 7.1 ± 0.3
2 mM PMS + 1 mM DDC

Fig. 3. A, erythrocyte K⁺ loss induced by oxygen free radicals. B, erythrocyte Na⁺ gain induced by oxygen free radicals.

Concentration and thus corresponds to a real increase in the basal K⁺ permeability. In addition, Fig. 8 shows that the increase in passive K⁺ permeability is not a "Gardos effect" because it is not affected by extracellular Ca²⁺, ethylene glycol bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid, quinine, or carbocyanin (23).

Fig. 9 shows that the inhibition of superoxide dismutase by DDC strongly enhances the effect of PMS on passive K⁺ permeability. This corresponds to a toxic effect of oxygen free radicals on the red cell membrane as further shown by the appearance of hemolysis at high PMS and DDC concentrations (Fig. 9 inset).

Inhibition of intracellular catalase by preincubation with 3-amino 1,2,4-triazole (29) had no effect on the PMS-dependent passive K⁺ permeability.

The PMS effect is slightly inhibited by addition of superoxide dismutase to the incubation medium (Table IV) and not modified by external catalase.

The Effect of DIDS on Passive K⁺ Permeability and NBT Reduction in PMS-treated Erythrocytes—It has been shown that the very active anion carrier of human red cells is able to

Fig. 4. Dose-response curves of the different transmembrane pathways for Na⁺ and K⁺ as a function of PMS concentration. The most affected parameter is the passive K⁺ permeability.

Fig. 5. Inhibition of the maximal rate of (Na⁺,K⁺)-pump by oxygen free radicals. Theoretical curves were constructed by the method described in Ref. 21 using $K_N = 3.1$ mmols/liters of cells and different maximal pump rates.

Fig. 6. Inhibition of the maximal rate of (Na⁺,K⁺)-cotransport by oxygen free radicals. Theoretical curves were constructed by the method described in Ref. 22 using $K_N$ for Na⁺ = 10 mmol/liters of cells, Hill's $n = 1.5$, and different maximal cotransport rates.
Oxygen Free Radicals and Erythrocyte K⁺ Loss

FIG. 7. Passive K⁺ permeability in PMS-treated erythrocytes as a function of the internal K⁺ concentration.

FIG. 8. The effect of inhibitors of the Gardos effect (quinine and carbocyanin) on the PMS-dependent increase in passive K⁺ permeability. See Ref. 23 for details under "Materials and Methods."

FIG. 9. Enhancement of PMS-dependent increase in passive K⁺ permeability by superoxide dismutase inhibition by DDC. External PMS concentration was 0.1 mM. Inset: hemolysis in erythrocytes treated with high PMS and DDC concentrations. MetHb absorbance was measured in (Na⁺K⁺)-Ringer medium. In Mg⁺++, sucrose medium the percentage of hemolysis is reduced suggesting a "free radical scavenger" effect of the sucrose.

FIG. 10. Interindividual variance in the effect of PMS on the different Na⁺ and K⁺ transport systems in human red cells.

TABLE IV
The effect of external superoxide dismutase on PMS-dependent increase of passive K⁺ permeability in human red cells

| Conditions          | PMS-dependent increase of passive K⁺ permeability (μmol liter⁻¹ of cells × %) | Control |
|---------------------|---------------------------------------------------------------------------------|---------|
| Control             | 3656 ± 40                                                                        |         |
| Superoxide dismutase|                                                                                 |         |
| 10 µg/ml            | 3662 ± 30                                                                        | 97 ± 2  |
| 30 µg/ml            | 3550 ± 125                                                                       | 88 ± 5  |
| 220 µg/ml           | 3035 ± 30                                                                        | 81 ± 2  |

TABLE V
The effect of DIDS on passive K⁺ permeability and NBT reduction in PMS-treated erythrocytes

Values in this table are given as mean ± range of duplicates. A similar result has been obtained in two other experiments.

| Conditions | PMS-dependent increase of passive K⁺ permeability (μmol liter⁻¹ of cells × %) | PMS-dependent NBT reduction (absorbance at 560 nm × %) | Inhibition |
|------------|-------------------------------------------------------------------------------|--------------------------------------------------------|------------|
| Control    | 3350 ± 80                                                                      | 143 ± 6                                               |            |
| DIDS       |                                                                               |                                                        |            |
| 5 µM       | 3812 ± 67                                                                      | 114 ± 4                                               | 121 ± 4    |
|            |                                                                               |                                                        | 15 ± 7     |
| 10 µM      | 4217 ± 17                                                                      | 126 ± 3                                               | 119 ± 6    |
|            |                                                                               |                                                        | 17 ± 9     |
| 30 µM      | 5417 ± 67                                                                      | 162 ± 4                                               | 107 ± 7    |
|            |                                                                               |                                                        | 20 ± 9     |

DISCUSSION

The results presented in this paper show that PMS treatment of human red cells results in a sustained generation of intracellular oxygen free radicals for more than 5 h. This phenomenon is partially masked by the very active erythro-
cyte superoxide dismutases which destroy such radicals (27). Indeed, superoxide dismutase inhibition by DDC reveals a significant production of oxygen free radicals in PMS-treated erythrocytes. The production of oxygen free radicals is further demonstrated by the appearance of MetHb. In fact, PMS treatment of human hemoglobin does not result in MetHb formation unless NADH is present in the incubation medium, suggesting a secondary reaction with oxygen free radicals.

The chemical nature of the erythrocyte substrates reacting with PMS is not yet completely understood. We observed here a decrease in the NADH content of PMS-treated erythrocytes under conditions in which glycolysis and thus NADH regeneration are inhibited by deoxyglucose. A likely mechanism of oxygen free radical production is the cyclic reaction shown previously in a cell-free system by Nishikimi et al. (19):

\[
\text{NADH} + \text{PMS (ox)} \rightarrow \text{NAD} + \text{PMS (red)}
\]

However, PMS may be reduced by other erythrocyte metabolites such as glutathione which exists at higher concentrations than that of NADH and is in redox equilibrium. This is at present under investigation.

The presence of oxygen free radicals is extremely noxious to the cell membrane. Several authors have reported peroxidation of unsaturated lipids by oxygen free radicals in different membrane preparations (13, 24-26). Indeed, we observed here that the PMS treatment of human red cells results in lipid peroxidation as shown by the increase in MDA above endogenous levels. The PMS-dependent membrane MDA is further increased by superoxide dismutase inhibition as expected for a lipid peroxidation dependent on the intracellular oxygen free radicals. On the other hand, lipid peroxidation is certainly not the only noxious effect of oxygen free radicals on the cell membrane. In fact, a small but significant fraction of the formed MetHb is firmly bound to the red cell membrane. A similar phenomenon has been previously described under conditions in which MetHb is produced in the presence of MDA, suggesting a cross-linkage mechanism between MDA, amino groups of MetHb, and amino groups of the membrane (26). The relative participation of lipid peroxidation, MetHb binding, and other mechanisms on the erythrocyte membrane damage induced by oxygen free radicals deserves further investigation.

The main purpose of this paper is the kinetic study of the effect of oxygen free radicals on the different K+ transport systems of human red cell membranes. Indeed, PMS treatment modifies the ionic equilibrium of human erythrocytes in a manner which resembles that previously observed under physiopathological conditions involving generation of oxygen free radicals (3-10). We observed that low PMS concentrations result in a quasi-specific increase in passive K+ permeability without any major effect on any specific K+ carrier such as the (Na+,K+)-pump, or the (Na+,K+)-cotransport system.

This increase in passive K+ permeability explains the cell K+ loss. It is certainly not a Garðs effect (28) because it is not inhibited by quinine, carbocyanin, or ethylene glycol bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid, nor is it carrier-mediated because it is independent of Cl-, which is thought to be a cosubstrate or cofactor of most carrier-mediated K+ transport systems. It thus appears likely to be the consequence of an increase in the K+ leak through the lipid bilayer. Indeed, the PMS-dependent increase in passive K+ permeability and cell K+ loss are both markedly increased by superoxide dismutase inhibition, further suggesting a mechanism involving the formation of transient K+ channels through membrane regions containing peroxidated phospholipids. The relative specificity for K+ has been previously observed under other circumstances (23) and may be explained by the fact that steric hindrance through the membrane channel is higher for the Na+ ion than for the K+ ion in the hydrated state.

It is interesting to note that sickled red cell membranes show a higher susceptibility to lipid peroxidation (31), increased binding of hemoglobin (32), and altered K+ permeability (33). Thus, these cells show some properties similar to our PMS-treated erythrocytes.

It appears from our results that PMS induces the intracellular generation of oxygen free radicals such as O2•-. The PMS-dependent O2•- can be released from the cells into the incubation medium by the anion carrier. This is shown by (i) a slight protective effect of external superoxide dismutase and (ii) an increase in PMS-dependent passive K+ permeability following inhibition of anion carrier by DIDS. These effects are difficult to explain. Lynch and Fridovich (38) proposed that in the absence of any O2•- scavenger in the external medium, internal and external O2•- are in equilibrium through the anion carrier. Thus the destruction of extracellular O2•- by superoxide dismutase would decrease the steady state level of

![Diagram](http://www.jbc.org/Downloaded from March 21, 2020)
intracellular O₂•. This in turn would decrease membrane peroxidation and cell K⁺ loss (28). The activity of exogenous or endogenous catalase does not modify the PMS-dependent passive K⁺ permeability. This result suggests that H₂O₂ is not an intermediary for the action of PMS on erythrocyte membranes (29-38). Conversely, the generation of H₂O₂ in the extracellular medium induces peroxidation and cell lysis (40). Further experiments are required in order to clarify the role of H₂O₂.

In conclusion, the PMS treatment of human red cells mimics the membrane peroxidation and K⁺ loss of certain physiological conditions in which oxygen free radicals are generated (Fig. 11). This system could thus represent a useful model for studying these mechanisms at the molecular level.

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