Oxidative stress in the human brain after subarachnoid hemorrhage

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Object. The aim of this study was to verify the patterns of antioxidant enzymatic activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in the human brain after subarachnoid hemorrhage (SAH) to verify whether an “oxidative stress situation” characterizes the brain response to subarachnoid bleeding.

Methods. Forty samples of gyrus rectus or temporal operculum that were obtained during a surgical approach to anterior circulation aneurysms were used for this study. The activity of total SOD, GSH-Px, and the SOD/GSH-Px ratio (which expresses the balance between the production of hydrogen peroxides by dismutation of superoxide radicals and the scavenging potential) were calculated in each case. Twelve samples were obtained from patients who underwent surgery for unruptured aneurysms (control group); 13 samples were obtained during surgical procedures performed within 72 hours of SAH; and 15 samples were obtained during delayed surgical procedures (> 10 days post-SAH). Ten patients presented with clinical deterioration caused by arterial vasospasm. In both SAH groups, mean total SOD activity was significantly higher than in the control group (p = 0.029). The mean activity of GSH-Px did not differ significantly between the SAH and control groups (p = 0.731). There was a significant increase in the SOD/GSH-Px ratio in both SAH groups, as compared with controls (p < 0.05). There was a significant correlation between the enzymatic activity and the clinical severity of the hemorrhage, with findings of lower values of SOD and, mainly, of the SOD/GSH-Px ratio in the poor-grade patients. The SOD/GSH-Px ratio was 2.14 ± 0.44 in patients who presented with clinical vasospasm and 1.24 ± 0.2 in cases without vasospasm.

Conclusions. The results of this study show an imbalance of the antioxidant enzymatic activities in the human brain after SAH, which is linked to the severity of the initial bleeding and possibly modified by the development of arterial vasospasm.

Key Words • subarachnoid hemorrhage • lipid peroxidation • vasospasm • superoxide dismutase • glutathione peroxidase

Despite recent advances in pharmacological treatment and improvement of surgical and anesthetic techniques, subarachnoid hemorrhage (SAH) from ruptured intracranial aneurysms still carries unacceptably high morbidity and mortality rates. The primary damage from SAH has received less attention than complications such as vasospasm and rebleeding; however, the immediate consequences of aneurysm rupture should be considered a fundamental step in producing brain damage. Direct studies of the neurochemical correlates of primary damage in the brain compartment after rupture of an intracranial aneurysm are limited to positron emission tomography, measurement of cerebral blood flow (CBF), and analysis of the mean consumption of oxygen; indirect data are also available from evaluation of cerebrospinal fluid (CSF) modifications of several markers or in experimental conditions. In most cases, the marked reduction in the cerebral metabolic rate of oxygen occurring after SAH is not coupled with the observed scant reduction of CBF and may also be independent of the hyperemic situation, with large quantities of oxygen available but a reduced need for consumption. On the basis of these data, a condition of oxidative stress has been postulated to occur after SAH, although it has never been demonstrated in a clinical setting.

In the brain compartment, there are protective systems against free radical production: superoxide radicals are inactivated by superoxide dismutase (SOD), and hydrogen peroxides produced in this reaction are scavenged by glutathione peroxidase (GSH-Px) and catalase; however, catalase appears to play a secondary role in hydrogen peroxide detoxification in the brain compared with other organs.

In a recent experimental study conducted by our group, the activity of both CuZn-SOD and Mn-SOD and GSH-
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Peroxidase (GSH-Px) was significantly decreased in the cerebral cortex of rats subjected to experimental SAH. In humans, however, the role of an imbalance of antioxidant enzymatic activities after SAH has never been investigated. The aim of this study was to examine the patterns of antioxidant enzymatic activities (SOD and GSH-Px) in the human brain after bleeding, to verify whether an oxidative stress situation characterizes the brain response to SAH.

Clinical Material and Methods

Tissue Samples

Forty samples of gyrus rectus or temporal operculum (volume < 0.5 ml) were obtained without the use of bipolar coagulation during surgical approaches to anterior circulation aneurysms. This study was approved by the Ethics Committees of the individual institutions involved. A consent form that gave a detailed list of specific problems associated with the surgical procedure was signed by the patient (or responsible person) before surgery.

Twelve patients underwent operations for unruptured aneurysms that had been found incidentally or had manifested with repeated transient ischemic attacks or cranial nerve palsy; these cases represented the control group. Twenty-eight patients were admitted after a diagnosis of SAH (within 72 hours of last bleeding in 20 cases). Their neurological condition on admission was assessed according to the modified Hunt and Hess classification, that is, the World Federation of Neurological Surgeons (WFNS) grading system. The extent of subarachnoid bleeding was categorized according to the computerized tomography (CT) classification proposed by Fisher, et al., and the classification proposed by Pasqualin, et al. Basal angiographic studies were obtained in most cases within 3 days of SAH, except in seven patients who underwent delayed surgery. All patients underwent serial transcranial Doppler (TCD) sonography studies at least every other day after SAH.

Patients with SAH were treated with intravenously administered nimodipine (24 mg/day) during the first 14 days posthemorrhage; steroids were never administered before surgery. All patients undergoing surgery in the delayed phase received tranexamic acid intravenously (6 g/day) until surgery; mannitol was used only in patients who experienced neurological deterioration caused by increased intracranial pressure or ischemic deficit from vasospasm. In all patients a postoperative angiographic study was obtained to verify the adequacy of aneurysm exclusion.

Vasospasm was assessed by angiographic studies and TCD measurements: symptomatic vasospasm was diagnosed when overt neurological deterioration occurred, accompanied by mean TCD velocities greater than 140 cm/second and/or significant arterial narrowing on angiographic studies. The patients’ outcomes were classified as favorable or unfavorable according to the criteria of the Glasgow Outcome Scale (GOS); favorable = good recovery or moderate disability).

Analytical Methods

In the operating room, brain samples of gyrus rectus or temporal operculum were carefully removed while avoiding thermal injury, gently washed in a precooled isotonic saline solution, and immediately frozen in dry ice and maintained at −80°C until analysis. Cortex slices were bound-cut, and then prepared in a prerefrigerated glovebox at −22°C. Brain samples were weighed (1/20 weight/volume) and homogenized (eight strokes up and down at 800 rpm) in 20 mM of ice-cold Tris-HCl (pH 7) in a precooled homogenizer. The protein content of the homogenate was assessed according to the method of Lowry, et al., with serum albumin as a standard. An aliquot of the homogenate was centrifuged at 6500 rpm for 20 minutes and used to evaluate enzymatic activities.

The total SOD activity was assayed, evaluating its ability to inhibit superoxide radical–dependent reactions in reducing cytochrome C, according to the procedures of Chan, et al., and Crapo, et al. The SOD activity is defined as micrograms of the SOD standard equivalent. The normal brain contains both cytosolic CuZn-SOD and mitochondrial Mn-SOD. The total SOD activity was measured with 10 μM of KCn in incubation medium to inhibit cytochrome C oxidase activity. The GSH-Px assay was performed as proposed by Brand, et al. The rate of disappearance of the reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH) at 340 nm was assessed using spectrophotometry. One unit of GSH-Px was defined as the amount of the enzyme necessary to oxidize 1 μmol NADPH/minute at pH 7.0 at 25°C.

Statistical Analysis

The data are expressed as the mean ± standard error of the mean (SEM). A statistical evaluation for intergroup comparison was performed using the one-way analysis of variance (ANOVA) and Scheffe’s test for multiple comparisons. Alternatively, when indicated, Student’s t-test of unpaired data with Bonferroni correction was conducted; the Spearman correlation was used to verify a possible relation between enzymatic activities and clinical grade at admission; statistical significance was accepted at a probability level of less than 0.05.

Results

Clinical Data

Forty patients (23 women and 17 men, mean age 54 ± 6 years) who underwent surgery for aneurysms of the anterior circulation were included in this study. Twelve of the 40 patients underwent operations for unruptured aneurysms and were included as controls. Among the 28 patients with ruptured aneurysms, 18 were classified in good neurological condition according to the WFNS grading system (Grades I and II), whereas 10 patients were considered to be in poor condition (Grades III and IV). As soon as possible after admission CT scans were obtained and showed a thin subarachnoid deposition of blood in seven cases, a thick subarachnoid deposition in 14 cases, and an intraventricular or intracerebral hematoma in seven cases. In 22 cases the aneurysm was on the anterior communicating artery ([ACA]; six unruptured and 16 ruptured aneurysms); in nine cases on the middle cerebral artery ([MCA]; five unruptured and four ruptured); and in nine cases on the internal carotid artery/posterior commu-
TABLE 1
Antioxidant activities and SOD/GSH-Px ratio in connection with the site of brain tissue sampling and the presence or absence of SAH in 40 patients with aneurysms

<table>
<thead>
<tr>
<th>Source of Sample</th>
<th>No. of Patients</th>
<th>SOD</th>
<th>GSH-Px</th>
<th>SOD/GSH-Px</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gyrus rectus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>6</td>
<td>48.93 ± 6.25</td>
<td>70.05 ± 6.0</td>
<td>0.67 ± 0.04</td>
</tr>
<tr>
<td>RA</td>
<td>16</td>
<td>93.49 ± 15.11</td>
<td>74.46 ± 8.57</td>
<td>1.33 ± 0.21</td>
</tr>
<tr>
<td>Temporal operculum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>6</td>
<td>49.37 ± 12.25</td>
<td>57.04 ± 13.38</td>
<td>0.87 ± 0.05</td>
</tr>
<tr>
<td>RA</td>
<td>12</td>
<td>95.01 ± 12.82</td>
<td>64.34 ± 8.89</td>
<td>1.88 ± 0.41</td>
</tr>
<tr>
<td>Total cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>12</td>
<td>49.15 ± 6.56</td>
<td>63.54 ± 7.26</td>
<td>0.77 ± 0.04</td>
</tr>
<tr>
<td>RA</td>
<td>28</td>
<td>94.14 ± 10.06†</td>
<td>70.12 ± 6.17</td>
<td>1.56 ± 0.21</td>
</tr>
</tbody>
</table>

* Values are expressed as enzymatic U/mg of protein, mean ± SEM. Abbreviations: RA = ruptured aneurysm; UA = unruptured aneurysm.
† p < 0.01 compared with unruptured aneurysms.
‡ p < 0.05 compared with unruptured aneurysms (Student’s t-test with Bonferroni correction). The difference between samples obtained from the gyrus rectus or temporal operculum (considering the presence or absence of hemorrhage) was not significant.

TABLE 2
Antioxidant activities and SOD/GSH-Px ratio in connection with the location of ruptured aneurysms

<table>
<thead>
<tr>
<th>Aneurysm Location &amp; Status</th>
<th>No. of Patients</th>
<th>SOD</th>
<th>GSH-Px</th>
<th>SOD/GSH-Px</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACoA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unruptured</td>
<td>6</td>
<td>48.93 ± 6.25</td>
<td>70.05 ± 6.0</td>
<td>0.67 ± 0.04</td>
</tr>
<tr>
<td>Ruptured</td>
<td>16</td>
<td>93.49 ± 15.11</td>
<td>74.46 ± 8.57</td>
<td>1.33 ± 0.21</td>
</tr>
<tr>
<td>MCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unruptured</td>
<td>5</td>
<td>48.66 ± 15.0</td>
<td>57.06 ± 16.4</td>
<td>0.85 ± 0.06</td>
</tr>
<tr>
<td>Ruptured</td>
<td>4</td>
<td>121.7 ± 21.7</td>
<td>47.43 ± 9.7</td>
<td>2.95 ± 0.8</td>
</tr>
<tr>
<td>ICA/PCoA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unruptured</td>
<td>1</td>
<td>52.91</td>
<td>56.92</td>
<td>0.93</td>
</tr>
<tr>
<td>Ruptured</td>
<td>8</td>
<td>81.68 ± 14.5</td>
<td>72.8 ± 11.6</td>
<td>1.4 ± 0.4</td>
</tr>
</tbody>
</table>

* Values are expressed as enzymatic U/mg of protein, mean ± SEM. According to ANOVA and Scheffé tests for multiple comparisons, no significant difference was found between the different aneurysm locations in the two subgroups (ruptured and unruptured aneurysms).

TABLE 3
Antioxidant activities and SOD/GSH-Px ratio in connection with the WFNS grade at admission in the group of patients in whom SAH was diagnosed

<table>
<thead>
<tr>
<th>WFNS Grade</th>
<th>No. of Patients</th>
<th>SOD</th>
<th>GSH-Px</th>
<th>SOD/GSH-Px</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>9</td>
<td>95.84 ± 14.68</td>
<td>58.36 ± 11.14</td>
<td>2.05 ± 0.49</td>
</tr>
<tr>
<td>II</td>
<td>9</td>
<td>103.02 ± 19.43</td>
<td>59.38 ± 3.16</td>
<td>1.78 ± 0.37</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>94.20 ± 37.0</td>
<td>85.66 ± 19.73</td>
<td>0.99 ± 0.20</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>75.05 ± 13.86</td>
<td>95.18 ± 15.25</td>
<td>0.87 ± 0.19</td>
</tr>
</tbody>
</table>

* Statistical analysis shows a significant trend toward increasing GSH-Px activity and a declining SOD/GSH-Px ratio in poor-grade patients (Spearman correlation: p = 0.43 for SOD; p = 0.012 for GSH-Px; p = 0.044 for SOD/GSH-Px.).

Enzymatic Activities: Total SOD

The enzymatic activity was significantly higher in samples obtained in patients who underwent operation after aneurysm rupture (Table 1). The difference in SOD activity was not significant when considering the different site of brain sampling. In the group of patients admitted after SAH, the difference in SOD activity was not significant when considering the aneurysm location (Table 2) or the WFNS grade at admission (Table 3). The SOD activity was significantly higher (p = 0.03) in patients presenting with thin subarachnoid blood clots than in patients with intraventricular bleeding and intracerebral hematoma (Table 4). Figure 1 shows the activity of SOD in controls (unruptured aneurysms), patients treated surgically within 72 hours of SAH, and patients who underwent delayed surgery. A significant difference was noted between the groups (p = 0.029): in particular, the enzymatic activity was significantly higher in the SAH groups than in controls and slightly higher in patients with early compared with delayed surgery. Patients with symptomatic vasospasm had significantly higher SOD activity than patients without vasospasm (Table 5), and although the difference in SOD activity between these groups was still marked when we considered the groups of patients who underwent early and delayed surgery separately, the difference did not reach statistical significance. Moreover, SOD levels were highest in the subgroup of patients with vasospasm who underwent early surgery. Finally, the SOD activity did not differ in patients with favorable outcomes compared with patients in whom unfavorable outcomes were found at 3-month follow-up examination (Table 6).

Enzymatic Activities: GSH-Px

The enzymatic activity was not significantly different in unruptured and ruptured aneurysms, and, moreover, there was no significant difference in GSH-Px activity associated with the site of brain sampling (Table 1). In the group of patients who were admitted after SAH, no significant difference in GSH-Px activity was noted in connection with the aneurysm location (Table 2), when the WFNS grade at admission was considered, we found a significant trend toward a higher activity of the enzyme in poor-grade patients (Table 3). Moreover, the GSH-Px activity did not differ significantly, either when CT data were considered (Table 4) or when the occurrence of symptomatic vaso-
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**TABLE 4**

Antioxidant activities and SOD/GSH-Px ratio in patients classified according to Fisher’s criteria*

<table>
<thead>
<tr>
<th>Clot Thickness</th>
<th>No. of Patients</th>
<th>SOD</th>
<th>GSH-Px</th>
<th>SOD/GSH-Px</th>
</tr>
</thead>
<tbody>
<tr>
<td>thin SAH</td>
<td>7</td>
<td>111.0 ± 17.14</td>
<td>62.91 ± 13.08</td>
<td>2.07 ± 0.42</td>
</tr>
<tr>
<td>thick SAH</td>
<td>14</td>
<td>94.74 ± 17.42</td>
<td>71.88 ± 10.13</td>
<td>1.57 ± 0.56</td>
</tr>
<tr>
<td>intraventricular hematoma</td>
<td>7</td>
<td>76.10 ± 10.48†</td>
<td>73.82 ± 7.5</td>
<td>1.05 ± 0.12‡</td>
</tr>
</tbody>
</table>

* Statistical analysis was performed using ANOVA and Student’s t-test for unpaired data with Bonferroni correction. The ANOVA results were as follows: † p = 0.03 compared with thin SAH (SOD activity); p = 0.825 (GSH-Px activity); p = 0.043, ‡ p = 0.05 compared with thin SAH (SOD/GSH-Px activity).

Increased patients with thin clots compared with intraventricular and/or intracerebral bleeding (Table 4). The activity of GSH-Px did not differ significantly when control patients were compared with patients who underwent early or delayed surgery (p = 0.731), as shown in Fig. 1.

**The SOD/GSH-Px Ratio**

The SOD/GSH-Px ratio was significantly higher in samples obtained after SAH (p = 0.05, Fig. 2). No significant difference was found in the SOD/GSH-Px ratio after allowing for the site of brain sampling (Table 1). In the group of patients admitted after their SAH, no significant difference was noted in the SOD/GSH-Px ratio after allowing for the different aneurysm location (Table 2). The SOD/GSH-Px ratio was significantly higher (p = 0.05) in patients admitted in good neurological condition (WFNS Grades I and II) after SAH (1.92 ± 0.3), compared with poor-grade patients (WFNS Grades III and IV, 0.93 ± 0.13; Table 3). The SOD/GSH-Px ratio was significantly increased in patients with thin clots compared with intraventricular and/or intracerebral bleeding (Table 4). In terms of the occurrence of symptomatic vasospasm, the SOD/GSH-Px ratio was significantly higher in patients in whom clinical vasospasm was diagnosed than in uncomplicated cases; the trend was more striking when we studied patients who underwent surgery in the early stage after SAH (Table 5). No significant difference in the SOD/GSH-Px ratio was observed between any of the groups when the outcome of patients was taken into account (Table 6).

**Discussion**

A few recent clinical studies were planned with the aim of verifying if neuronal damage caused by SAH might be significantly reduced using antioxidant pharmacological strategies. However, direct evidence of an oxidative stress occurring in the human brain after SAH has never been obtained. Experiments have demonstrated that the direct effect of subarachnoid bleeding induces a primary change in the oxidative mechanism due to a significant impairment of the mitochondrial function and a significant reduction of the antioxidant enzymatic systems, mainly in the acute stage after SAH. In this situation the

**TABLE 5**

Antioxidant activities and SOD/GSH-Px ratio in patients with or without symptomatic vasospasm*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>SOD</th>
<th>GSH-Px</th>
<th>SOD/GSH-Px</th>
</tr>
</thead>
<tbody>
<tr>
<td>vasospasm</td>
<td>10</td>
<td>118.09 ± 15.27†</td>
<td>67.19 ± 7.67</td>
<td>2.14 ± 0.44‡</td>
</tr>
<tr>
<td>early surgery</td>
<td>4</td>
<td>139.31 ± 13.88</td>
<td>63.28 ± 18.55</td>
<td>2.09 ± 1.20 ‡</td>
</tr>
<tr>
<td>delayed surgery</td>
<td>6</td>
<td>103.94 ± 22.85</td>
<td>69.79 ± 5.95</td>
<td>1.63 ± 0.42</td>
</tr>
<tr>
<td>no vasospasm</td>
<td>18</td>
<td>80.84 ± 12.34</td>
<td>71.75 ± 8.73</td>
<td>1.24 ± 0.2</td>
</tr>
<tr>
<td>early surgery</td>
<td>9</td>
<td>78.77 ± 20.71</td>
<td>76.42 ± 15.17</td>
<td>1.20 ± 0.93</td>
</tr>
<tr>
<td>delayed surgery</td>
<td>9</td>
<td>82.90 ± 14.73</td>
<td>67.07 ± 9.35</td>
<td>1.29 ± 0.24</td>
</tr>
</tbody>
</table>

* Statistical analysis was performed using ANOVA and Student’s t-test for unpaired data with Bonferroni correction. † p = 0.05 compared with thin SAH. ‡ p = 0.05 compared with no vasospasm.

![Bar graph showing the mean level of antioxidant enzymatic activities (± SEM) in tissue samples of gyrus rectus or temporal operculum obtained during surgery for anterior circulation aneurysms. Enzymatic activities are expressed as enzymatic U/mg of protein (prot.). There is a significant difference between groups (p = 0.03); SOD activity is significantly higher in both SAH groups than in control patients undergoing operation for unruptured aneurysms (***p = 0.02). The activity of GSH-Px does not significantly differ within the three groups (p = 0.73).](Image 92x158 to 258x306)

![J. Neurosurg. / Volume 89 / November, 1998 751](Image 157x648 to 532x924)
leakage of superoxides in the mitochondrial electron transfer chain may be responsible for the enhancement of peroxidative reactions. The enhanced production and activity of the reactive oxygen type plays an important role in the pathogenesis of neuronal damage and arterial vasospasm after SAH.

The theory of an oxidative stress in humans after SAH is based only on indirect data: increased levels of some markers of lipid peroxidative processes (such as arachidionate metabolites and particularly metabolites of the lipoxygenase pathway) were found in the cisternal CSF after SAH in previous studies, and an enhanced ex vivo production of leukotrienes and prostaglandins was demonstrated when evaluating the metabolic capacity of gyrus rectus samples obtained during surgery for aneurysms of the ACoA. In the cisternal CSF, SOD levels were significantly reduced after SAH, although they were significantly higher in patients who presented with symptomatic vasospasm. According to a previous report by Strand and Marklund, in patients with cerebral ischemia these changes can be regarded as CSF markers of an ischemic situation. However, when considered all together, these data are not sufficient to establish an effective role of the lipoperoxidative processes in the pathogenesis of primary brain damage after SAH.

This study was undertaken to verify whether SAH causes a significant impairment of the antioxidative enzymatic capacities of the human brain. An important issue concerns the balance between SOD and GSH-Px activities: during aging the SOD/GSH-Px ratio in the brain increases because of the rise in SOD activity, consequently increasing production of lipoperoxides. Superoxide dismutase and GSH-Px are the most important enzymatic antioxidant systems present in the brain tissue: in physiological conditions, there is a balance between the production of hydrogen peroxide during dismutation of superoxide radicals, and the detoxifying activity of GSH-Px. This ratio, independently of the absolute values of enzymatic activities, represents an important index of the oxidative pattern. However, the results of our study demonstrate that a significant imbalance in these systems develops after SAH in brain tissue, leading to increased SOD activity and an increased SOD/GSH-Px ratio.

In patients who present in good neurological condition (WFNS Grade I and II) and in patients with thin SAH on CT scanning, the SOD activity is particularly elevated, indicating an increased production of superoxide radicals that is not matched by the upregulation of GSH-Px activity. It is well known that, in the acute stage of SAH, patients in good clinical condition have a characteristic uncoupling between CBF values, which are close to normal, and a depressed cerebral metabolism, with a peculiar hyperemic pattern and a reduced arteriovenous oxygen difference, which leads to a high availability of oxygen and a reduced capacity to utilize it, that is, an oxidative stress condition.

The reason for this metabolic impairment is not completely understood: Fein suggested that changes in cerebral metabolism after SAH might be related to a primary toxic effect elicited by the presence of blood in the subarachnoid cisterns, through the activation of a neural mechanism. In previous experimental studies, our group showed that the observed impairment of mitochondrial function was unrelated to the amount of subarachnoid blood in the basal cisterns or to the modifications of intracranial pressure (depending on the volume of blood injected). This is the case when the SOD/GSH-Px ratio found in patients with thin subarachnoid blood might be explained by the existence of an uncoupling between CBF and energy metabolism. On the other hand, patients with intraventricular bleeding or intracerebral hematoma (those in poor neurological condition) the reduction of CBF elicited by the increase in intracranial pressure and the decreased metabolic rate may be closely related, according to Jakobsen, et al. In similar conditions oxygen availability is reduced and SOD and the SOD/GSH-Px ratio may be lower than in other groups because of a relatively higher activity of GSH-Px. Apart from the severity of the initial hemorrhage (as indicated by the WFNS grade), other factors such as the aneurysm location or the site of brain tissue sampling are not influential in determining changes in enzymatic activities. As for the surprising, although not significant, decrease in SOD activity and SOD/GSH-Px ratio observed in patients with thick subarachnoid clots, it should be noted that metabolic changes in the tissue compartment are probably independent of changes occurring in the CSF compartment described previously by other authors. The tissue changes reported in connection with thick cisternal clots in our study are more likely explained by the high percentage of poor-grade patients and the aforementioned trend of decreased enzymatic activity. The present results indicate that the modifications in the antioxidant activities remain relatively stable after the early stage, with a progressive nonsignificant decrease in SOD activity and the SOD/GSH-Px ratio observed in the samples obtained at delayed surgery.

When considering the secondary insult caused by vasoospasm, an important question arises about the role of ischemia in determining an impairment in brain function. The
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results of clinical and experimental studies have shown that, even if the reduction of arterial diameter reaches 33%, no significant effects on CBF are produced; although a decrease in CBF may develop in a minority of cases (5–10%), this reduction may be compensated by a sufficient increase in arteriovenous oxygen difference. Only when a critical level is reached does the cerebral metabolic rate of oxygen decrease, with consequent impairment of neuronal function and the onset of neurological deterioration. The data in this study show a significant increase in the SOD/GSH-Px ratio in patients with vasospasm, with this increase linked to the very high SOD activity found in the subgroup of patients who underwent early operation (139.31 ± 13.88) and the relatively high SOD activity found in the delayed operation subgroup (103.94 ± 22.85). This indicates that in those patients who underwent operation early after SAH and who later developed symptomatic vasospasm, a severe oxidative stress situation was already present at the time of surgery (that is, before the onset of ischemic symptoms) and was more dependent on modifications of SOD than of GSH-Px activity. Thus, the increase in SOD activity and of the SOD/GSH-Px ratio observed in the early stage after SAH might be considered to be not only a consequence of the uncoupling between the reduction of CBF and metabolism, but also a risk factor for the development of subsequent ischemic complications from vasospasm.

Conclusions

In a clinical setting, the present data support the hypothesis of the existence of an oxidative stress in the human brain after rupture of an intracranial aneurysm, showing that: 1) the antioxidant enzymatic perturbation in the tissue is mainly related to the severity of the initial SAH and not to the aneurysm location or the thickness of subarachnoid blood clots; 2) after the initial insult, the modifications of the antioxidant enzymatic activities remain relatively stable, with the SOD/GSH-Px ratio clearly depicting the unbalanced situation; and 3) a characteristic increase in SOD precedes the occurrence of symptomatic vasospasm in patients undergoing operation in the early stage after SAH, and the SOD activity remains relatively high even after the development of vasospasm.

References


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