A New Approach to the Integrity of Dual Blood–Brain Barrier Functions of Global Ischemic Rats
Barrier and Carrier Functions

Hideyuki Yoshizumi, MD; Yasuhisa Fujibayashi, PhD; and Haruhiko Kikuchi, MD, PhD

Background and Purpose: We studied the influence of reperfusion on carrier and barrier functions of the blood–brain barrier after transient global ischemia in rats.

Methods: We used iodine-125–labeled 3-iodo-α-methyl-L-tyrosine and carbon-14–labeled sucrose as tracers for studying carrier and barrier functions of the blood–brain barrier, respectively. Brain uptakes of two tracers were measured in Wistar rats subjected to either 15- or 30-minute four-vessel occlusion developed by Pulsinelli and Brierly before recirculation for 3, 6, 24, 48, and 72 hours. Tracer (5 μCi) was injected intravenously in each rat 30 minutes before killing the animal.

Results: Following 15- or 30-minute ischemia, [14C]sucrose uptakes were significantly higher at 3 and 6 hours of reperfusion before recovery to control values after reperfusion for 24 to 48 hours in almost all brain regions. However, a rebound in radioligand uptake was significantly manifested in some sites at 72 hours after reperfusion (p<0.05 to p<0.01). Uptakes of 125I-3-iodo-α-methyl-L-tyrosine were brain site–dependent: significantly (p<0.05) higher in cortex (3 and 48 hours after reperfusion) and thalamus (3, 6, and 48 hours after reperfusion) but significantly (p<0.05 to p<0.01) lower in striatum, cortex (72 hours after reperfusion), and midbrain (6, 24, and 72 hours after reperfusion). Because the [14C]sucrose uptake in brain was 10% lower than that of 125I-3-iodo-α-methyl-L-tyrosine, the change in absolute transport of the latter tracer was approximated to its brain uptake.

Conclusions: The carrier and barrier functions of the blood–brain barrier should be evaluated separately. The radioligand 125I-3-iodo-α-methyl-L-tyrosine may serve as a useful tool to evaluate the carrier function of the blood–brain barrier after transient cerebral ischemia in rats. (Stroke 1993;24:279–285)

KEY WORDS • blood–brain barrier • cerebral ischemia • reperfusion • rats

It has been recognized that the integrity of the blood–brain barrier (BBB) may have an important influence on the subsequent pathophysiology and treatment of cerebral ischemia. In addition to evaluations of the effects of reperfusion on BBB permeability to protein tracers, various studies have shown transient and/or permanent opening of the BBB to albumin (large protein tracer) and α-aminoisobutyric acid (small protein tracer).

The BBB has a dual function: 1) prevention of circulating toxic agents and osmotically active proteins from entering the central nervous system (carrier function) and 2) transportation of essential nutrients, hormones, and drugs to the brain and elimination of metabolites from the brain (carrier function). Thus, to evaluate alterations in the functional integrity of the BBB during occlusion/reperfusion, it may be useful to study these functions separately.

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(LNAAs) transport system6 (with no affinity to other subsequent metabolic pathways), we used this radioligand to study the carrier function of BBB. In other words, we can postulate the amino acid carrier function of BBB from the basis of I-AMT accumulation in brain.

By the use of these two tracers, we successfully evaluated the dual function of the BBB in the four-vessel occlusion/reperfusion rat model of Pulsinelli and Brierly.7

Methods

Experimental Design

Of a total of 60 male Wistar rats (200–250 g), 57 animals were used. Transient global ischemia was achieved by subjecting the rats to either 15-minute (group A, n=25; five cases were allowed for each recirculation interval) or 30-minute (group B, n=25; five cases were allowed for each recirculation interval) occlusion followed by 3, 6, 24, 48, and 72 hours of recirculation intervals for both groups. As controls (n=5), rats were sham-operated under similar operative conditions but were not subjected to any occlusions. After subjecting the animals to 30-minute ischemia (group B), two rats died at 48 and 72 hours after reperfusion. These two subjects were replaced by using two of the five rats reserved for any such anticipated losses. Rats that showed signs of fits were excluded.

Preparation of Global Ischemic Rats

Transient global cerebral ischemia in rats was inflicted according to the method of Pulsinelli and Brierly.7 Briefly, 1 day before the experiment, both common carotid arteries of diethyl ether–anesthetized rats were surgically exposed through a ventral, midline cervical incision. An atrumatic arterial clasp (clasp pressure, 20–25 g) was placed loosely around each common carotid artery without interrupting the carotid blood flow, and the incision was closed with silk sutures. A second incision, 1 cm in length, was made posterior to the occipital bone overlying the first two cervical vertebrae. With the aid of an operating microscope, the right and left alar foramina of the first cervical vertebra were exposed. A 0.5-mm-diameter electrocautery needle (Bovie Monopolar Electrocautery, Cincinnati, Ohio) was inserted through each alar foramen, and both vertebral arteries were subsequently occluded by electrocautery.

The rats recovered without sequelae 1 to 2 hours later; they were fasted overnight but were allowed free access to water. On the next day, awake rats were anesthetized with diethyl ether, and ventral neck sutures were removed while the animals were held loosely. Both carotid clamps were then tightened to effect vascular occlusion. During the course of performing vascular occlusion the animals remained unconscious and indicated no signs of pain or suffering. The behavior of the rats was observed during the occlusion period. Only those animals that did not show a righting response to manually applied pressure on the tail were subjected to further experiments.

During ischemia, the left femoral artery and vein were cannulated; arterial blood pressure was monitored with a pressure transducer (Biophysiograph 180 system, San-Ei Instrument, Tokyo) and traced with a pen oscillograph recorder (8K-221-S, San-Ei). Arterial blood was sampled anaerobically, and PaO2, PaCO2, and pH were measured with a blood gas analyzer (ABL 30; Radiometer, Copenhagen, Denmark). The pH value was corrected whenever necessary with intravenous infusion of sodium bicarbonate solution. The body temperature was maintained at 37°C by a thermostat-regulated warming device.

Successful four-vessel occlusion was confirmed by the recorded electroencephalogram (Nihon Koden, Tokyo) becoming isoelectric within a few seconds of clamping the carotid arteries. Clips were then removed after either 15- or 30-minute occlusion, and patency of the carotid arteries was confirmed by a constant stream of blood flow visually.

Preparation of 125I-AMT was conducted as described previously by using 125I-NaI (Amersham Japan, Tokyo).

Determination of Plasma and Tissue Tracer Concentrations

Groups of three intact rats each were killed at 5, 10, 15, 30, and 60 minutes after intravenous administration of 125I-AMT, and the time course of brain accumulation of 125I-AMT was pursued. Animals were killed at 30 minutes after intravenous 125I-AMT because brain accumulation of this radioligand was highest at this time interval after injection.

Tissue samples were analyzed by the full-spectrum, dual-label disintegrations per minute method (Packard Instrument S.A., Zurich, Switzerland) using [16O]toluene (Packard) and 125I-AMT quenching standards. This is a method to calculate the respective activities of the individual radionuclides of dual-labeled samples. Each animal received both intravenous 125I-AMT (5 µCi) and [14C]sucrose of specific activity 4.4 mCi/mmol (New England Nuclear, Dreieich, FRG) concomitantly through the tail vein. Thirty minutes after tracer administration, arterial blood samples were collected. The tracer level in 0.1 ml plasma was measured with a liquid scintillation counter (1900CA, Packard). The rats were decapitated, and the brains were promptly isolated. Pial vessels and choroid plexus were removed before dissecting the brain into the following eight regions on an ice-cold glass cover: cerebellum, hippocampus, striatum, cerebral cortex, midbrain, thalamus, andpons. These brain sites were immediately weighed and put into their respective vials. One milliliter of Nuclear Chicago tissue solubilizer (Amersham Japan) was added to each vial before incubating overnight at 55°C. This was followed by adding 6 ml of toluene scintillator containing 2,5-diphenyloxazole and 2,2'-p-phenylenebis(5-phenyloxazole) in the vial. Radioactivity counts were measured with a liquid scintillation counter (1900CA, Packard). Quench and background counts were corrected with an external standard. The amino acid transport index (ATI) was calculated by the following equation:

$$L = Cp(A) \times \frac{Cb(S)}{Cp(S)}$$

$$\text{ATI} = \frac{Cb(A) - L}{Cp(A)} = \frac{Cb(A)}{Cp(A)} - \frac{Cb(S)}{Cp(S)}$$
TABLE 1. [14C]Sucrose Accumulation in Rat Brain After 15 (Group A) or 30 (Group B) Minutes of Transient Global Ischemia

<table>
<thead>
<tr>
<th>Brain site</th>
<th>Group</th>
<th>Control</th>
<th>3</th>
<th>6</th>
<th>24</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellum</td>
<td>A</td>
<td>0.031±0.016</td>
<td>0.080±0.028*</td>
<td>0.068±0.018*</td>
<td>0.043±0.006</td>
<td>0.037±0.010</td>
<td>0.049±0.018</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>...</td>
<td>0.062±0.016*</td>
<td>0.073±0.014†</td>
<td>0.038±0.008</td>
<td>0.041±0.006</td>
<td>0.058±0.008*</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>A</td>
<td>0.023±0.014</td>
<td>0.094±0.020†</td>
<td>0.059±0.020*</td>
<td>0.036±0.007</td>
<td>0.038±0.007</td>
<td>0.046±0.021*</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>...</td>
<td>0.064±0.022†</td>
<td>0.072±0.010†</td>
<td>0.025±0.007</td>
<td>0.030±0.007</td>
<td>0.056±0.028*</td>
</tr>
<tr>
<td>Striatum</td>
<td>A</td>
<td>0.013±0.014</td>
<td>0.058±0.020†</td>
<td>0.055±0.023†</td>
<td>0.034±0.005*</td>
<td>0.014±0.012</td>
<td>0.024±0.020</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>...</td>
<td>0.058±0.018†</td>
<td>0.071±0.017†</td>
<td>0.018±0.016</td>
<td>0.030±0.007*</td>
<td>0.042±0.025</td>
</tr>
<tr>
<td>Cortex</td>
<td>A</td>
<td>0.032±0.020</td>
<td>0.041±0.039</td>
<td>0.060±0.020</td>
<td>0.038±0.004</td>
<td>0.037±0.006</td>
<td>0.040±0.019</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>...</td>
<td>0.067±0.029</td>
<td>0.059±0.007*</td>
<td>0.019±0.016</td>
<td>0.040±0.009</td>
<td>0.054±0.019</td>
</tr>
<tr>
<td>Midbrain</td>
<td>A</td>
<td>0.019±0.017</td>
<td>0.061±0.039</td>
<td>0.053±0.032</td>
<td>0.036±0.016</td>
<td>0.000±0.000</td>
<td>0.030±0.026</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>...</td>
<td>0.049±0.037</td>
<td>0.069±0.011†</td>
<td>0.027±0.025</td>
<td>0.013±0.014</td>
<td>0.075±0.030†</td>
</tr>
<tr>
<td>Thalamus</td>
<td>A</td>
<td>0.035±0.006</td>
<td>0.076±0.015†</td>
<td>0.059±0.023</td>
<td>0.033±0.010</td>
<td>0.018±0.016</td>
<td>0.029±0.020</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>...</td>
<td>0.045±0.029</td>
<td>0.067±0.011†</td>
<td>0.015±0.023</td>
<td>0.025±0.012</td>
<td>0.038±0.015</td>
</tr>
<tr>
<td>Pons</td>
<td>A</td>
<td>0.035±0.013</td>
<td>0.072±0.018†</td>
<td>0.057±0.010*</td>
<td>0.035±0.003</td>
<td>0.026±0.016</td>
<td>0.028±0.005</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>...</td>
<td>0.054±0.018</td>
<td>0.052±0.018</td>
<td>0.008±0.006</td>
<td>0.037±0.008</td>
<td>0.034±0.011</td>
</tr>
</tbody>
</table>

Values are mean±SD. [14C]Sucrose was injected intravenously 30 minutes before decapitation. Each numerical value represents the ratio of brain to plasma radioactivity.

*p<0.05, †p<0.01 increase vs. sham-operated control rats.

where Cb(A) and Cb(S) define brain concentrations of 125I-AMT and [14C]Sucrose, respectively, and plasma levels of the former and latter were represented as Cp(A) and Cp(S), respectively. L represents the total brain concentration of permeated 125I-AMT and residual blood in brain by the end of the experiment.

**Statistical Analysis**

All results were expressed as mean±SD. Differences between groups were evaluated by analysis of variance followed by the Student’s t test for comparison between two-paired groups.

**Results**

Brain/plasma concentration ratios [Cb(S)/Cp(S)] of various brain sites for [14C]Sucrose are illustrated in Table 1 and Figure 1. When subjected to 15 minutes of ischemia, Cb(S)/Cp(S) was significantly (p<0.05 to p<0.01) elevated at 3 hours (in the cerebellum, hippocampus, striatum, thalamus, and pons), 6 hours (in the cerebellum, hippocampus, striatum, and pons), and 24 hours (in the striatum) after reperfusion. Recovery to control level was observed at either 24 or 48 hours after reperfusion. However, the ratio significantly (p<0.05) rebounded in the hippocampus at 72 hours after reperfusion.

Insult with 30 minutes of global ischemia significantly (p<0.05 to p<0.01) elevated the Cb(S)/Cp(S) ratio after 3 hours (in the cerebellum, hippocampus, and striatum) and 6 hours (in the cerebellum, hippocampus, striatum, cortex, midbrain, and thalamus) of reperfusion. The ratio recovered to the control level at 24 hours after reperfusion. However, the ratio returned to significantly (p<0.05 to p<0.01) high values at 48 hours (in the striatum) and 72 hours (in the cerebellum, hippocampus, and midbrain) after reperfusion.

With regard to the brain/plasma concentration ratio [Cb(A)/Cp(A)] of 125I-AMT (Table 2 and Figure 2), the value in the striatum decreased significantly (p<0.05) at 72 hours after reperfusion when rats were subjected to 30-minute ischemia. In the cortex, the ratio was significantly (p<0.05) higher at 3 hours (in both groups A and B) and at 48 hours (group A) after reperfusion and significantly (p<0.05) lower at 72 hours after reperfusion (group B). Unlike the cortex, the midbrain Cb(A)/Cp(A) was significantly (p<0.05 to p<0.01) lower at 6, 24, and 72 hours after reperfusion (in both groups A and B). In the thalamus, Cb(A)/Cp(A) was significantly (p<0.05) higher at 3 hours (in both groups A and B), 6
hours (group B), and 48 hours (group A) after reperfusion. At brain sites such as the cerebellum, hippocampus, striatum, and pons, no significant differences were verified.

Except for the cortex, regional changes in ATI (Table 3, Figure 3) were dependent on Cb(A)/Cp(A) at 48 hours (group A) and 3 hours (group B) after reperfusion. A similar phenomenon was observed in the thalamus 6 hours after reperfusion when rats were subjected to 30-minute ischemia (group B).

**Discussion**

Sucrose transport into the brain is restricted by the BBB, and it remains within the extracellular space even when it has unexpectedly crossed the BBB. In addition to being used for measuring regional blood volume, \(^{14}\text{C}\)sucrose can be used as a specific tracer for studying the integral characteristics of BBB. In our present study, cerebral accumulations of \(^{14}\text{C}\)sucrose at 3 to 6 hours after recirculation in rats (previously subjected to 15 or 30 minutes of ischemia) increased 1.5-fold to fivefold higher than the control value (Figure 1). This remarkable increase in brain \(^{14}\text{C}\)sucrose accumulation is an indication of the transient BBB opening, since the increase in the cerebral residual blood volume has been reported as negligible and only 12% at 3 and 24 hours after recirculation, respectively, when the rats were subjected to 30-minute ischemia. The BBB permeability found in the present study using \(^{14}\text{C}\)sucrose resembles previous findings using labeled sucrose, dextran, albumin, and other radioligands. The barrier function of BBB is dependent on the molecular size. In the present study, I-AMT showed an extremely high uptake in the brain and manifested completely different patterns compared with those of \(^{125}\text{I}\)-AMT (compare Table 1 with Table 2), although their molecular weights are approximately equal.

The amino acid transport across the BBB is materialized by three carrier systems. Among these, only the LNAA system transports most of the brain essential amino acids into the brain. Tyrosine, a precursor of neurotransmitters that is required for protein synthesis in the brain, shows a high affinity toward the LNAA system of the BBB in addition to indicating a high brain uptake index. The radioiodinated tyrosine analogue \(^{125}\text{I}\)-I-AMT has characteristics that allow it to serve as a selective transport marker for the LNAA system.

Cerebral I-AMT uptake included the residual blood volume and nonspecific leakage via the BBB. However, because a very low I-AMT concentration prevailed in
TABLE 3. Amino Acid Transport Index After 15 (Group A) or 30 (Group B) Minutes of Transient Global Ischemia

<table>
<thead>
<tr>
<th>Brain site</th>
<th>Group</th>
<th>Control</th>
<th>3</th>
<th>6</th>
<th>24</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellum</td>
<td>A</td>
<td>0.939±0.427</td>
<td>0.683±0.063</td>
<td>0.732±0.164</td>
<td>0.713±0.054</td>
<td>0.985±0.224</td>
<td>0.859±0.221</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td>0.970±0.241</td>
<td>0.709±0.171</td>
<td>0.584±0.217</td>
<td>0.683±0.172</td>
<td>0.566±0.158</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>A</td>
<td>1.040±0.522</td>
<td>0.818±0.072</td>
<td>0.853±0.286</td>
<td>0.719±0.099</td>
<td>1.068±0.180</td>
<td>0.865±0.287</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td>1.220±0.362</td>
<td>0.907±0.208</td>
<td>0.818±0.450</td>
<td>0.735±0.164</td>
<td>0.590±0.203</td>
</tr>
<tr>
<td>Striatum</td>
<td>A</td>
<td>1.280±0.461</td>
<td>1.110±0.209</td>
<td>0.968±0.208</td>
<td>0.820±0.175</td>
<td>0.820±0.506</td>
<td>1.166±0.323</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td>1.168±0.416</td>
<td>1.116±0.214</td>
<td>0.785±0.303</td>
<td>0.764±0.246</td>
<td>0.648±0.247*</td>
</tr>
<tr>
<td>Cortex</td>
<td>A</td>
<td>0.820±0.063</td>
<td>1.131±0.293†</td>
<td>0.880±0.187</td>
<td>0.747±0.140</td>
<td>1.028±0.178</td>
<td>0.895±0.267</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td>1.221±0.388</td>
<td>1.038±0.261</td>
<td>0.828±0.666</td>
<td>0.720±0.133</td>
<td>0.570±0.187*</td>
</tr>
<tr>
<td>Midbrain</td>
<td>A</td>
<td>2.170±0.534</td>
<td>1.642±0.582</td>
<td>1.028±0.392‡</td>
<td>1.071±0.203‡</td>
<td>2.203±0.529</td>
<td>1.362±0.402*</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td>1.712±0.808</td>
<td>0.975±0.305‡</td>
<td>0.751±0.308‡</td>
<td>1.498±0.784</td>
<td>1.306±0.127‡</td>
</tr>
<tr>
<td>Thalamus</td>
<td>A</td>
<td>0.736±0.063</td>
<td>0.832±0.059†</td>
<td>0.823±0.138</td>
<td>0.703±0.081</td>
<td>1.322±0.371†</td>
<td>0.969±0.418</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td>1.259±0.424†</td>
<td>0.980±0.237</td>
<td>0.764±0.389</td>
<td>0.941±0.381</td>
<td>0.664±0.187</td>
</tr>
<tr>
<td>Pons</td>
<td>A</td>
<td>0.729±0.148</td>
<td>0.608±0.078</td>
<td>0.626±0.075</td>
<td>0.670±0.058</td>
<td>0.944±0.157</td>
<td>0.876±0.333</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td>0.819±0.221</td>
<td>0.730±0.145</td>
<td>1.000±0.637</td>
<td>0.704±0.119</td>
<td>0.606±0.134</td>
</tr>
</tbody>
</table>

Values are mean±SD. Amino acid transport index was calculated as the equation shown in the text. *p<0.05 decrease, †p<0.05 increase, ‡p<0.01 decrease vs. sham-operated control rats.

The blood, these factors were not dominant enough to influence brain I-AMT accumulation. As a result, ATI, corrected with uptake and blood levels of [14C]sucrose, approximated well to the gross I-AMT uptake (Figure 2 and Figure 3). Moreover, regional blood flow affects the cerebral uptake of labeled compounds. In the case of I-AMT, however, the regional blood flow probably did not influence the cerebral accumulation because I-AMT accumulation in brain was a transient phenomenon (shown in our preliminary studies on normal rats). In addition, cerebral blood flow after temporal global ischemia recovers within a short period.1

From these findings, the carrier function should be evaluated separately from the barrier function of the BBB to better understand the effect of occlusion/reperfusion on BBB integrity. In addition, ATI (and presumably, gross I-AMT accumulation) may be considered as an appropriate parameter for assessing the carrier function (especially amino acid transport) of the BBB in the occlusion/reperfusion model. Generally, alterations of the barrier function of the BBB (illustrated by the [14C]sucrose) in the occlusion/reperfusion model are visualized as a unidirectional response compared with sham-operated rats, that is, an increase in permeability (Figure 1). However, the carrier function in certain brain sites manifested by 125I-AMT displayed a biphasic/bidirectional response, namely, suppression and acceleration of amino acid transport. Further, such responses varied with occlusion/reperfusion durations and brain regions (Figure 2) in rats inflicted with global ischemia. Veins and venules are the primary sites of disruption of the barrier function of the BBB,11 but the distribution or vulnerable site after ischemia/reperfusion of the LNAAsystem in cerebral vessels is still under investigation. Further studies are necessary to elucidate the different characteristics of the carrier and barrier functions of the BBB after transient global ischemia.

Tyrosine transport is an important limiting step in modulating catecholamine synthesis by regulating precursor availability. A change in I-AMT accumulation, namely tyrosine transport, might serve as a good index for functional alterations of the brain, although a detailed interpretation of the relation between tyrosine transport and brain activities cannot be concretely elucidated in the present study.

Assessing functional reversibility of the ischemic brain is considered an important approach for treatment. In the present study, prolongation of ischemia induced qualitative changes in the barrier and carrier functions of the BBB. Iodine-containing contrast media, gadolinium diethylenetriamine penta-acetic acid, and some other radioligands are used for x-ray computed

![Figure 3. Line graphs show regional amino acid transport index (ATI) after brain insult with either 15 or 30 minutes of transient global ischemia. Each numerical value is ratio of mean regional ATI at each reperfusion time to mean of control in cerebellum (○), hippocampus (●), striatum (△), cortex (□), thalamus (●), and pons (×).](http://stroke.ahajournals.org/Downloaded/figure3.png)
tomography, magnetic resonance imaging, or single-photon emission computed tomography, respectively, to visualize alterations of the barrier function in clinical medicine. Moreover, these methods are used primarily to detect the absence of barrier function, because cerebral accumulations of these diagnostic agents are too meager to detect the insignificant reversible changes in BBB. However, high $^{125}$I-AMT uptake into the brain improves the signal-to-noise ratio in the quantitative detection of BBB abnormalities.

In conclusion, the barrier function of ischemic animal models could be evaluated separately from the barrier function of BBB by using $^{125}$I-AMT. Gamma-emitting short half-life radionuclide iodine-123-labeled I-AMT has been proved to be a useful radioligand for imaging brain tumors, $^{13-16}$ melanomas, $^{13-16}$ and pancreas $^{17,18}$ in humans. In assessing BBB integrity, use of $^{125}$I-AMT with single-photon emission computed tomography would serve as a new approach to understanding the barrier function of BBB in human subjects with cerebral ischemia.

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References


Editorial Comment

The blood–brain barrier (BBB) minimizes the entry of molecules into brain tissue. This restriction is accomplished by tight junctions between adjacent endothelial cells and a paucity of pinocytic vesicles in the endothelium of arterioles, capillaries, venules, and veins. $^{1,2}$ Perturbations to the BBB, i.e., acute increases in arterial blood pressure and ischemia followed by reperfusion, increase the transport of molecules across the BBB. $^{3,4}$ Thus, changes in the integrity of the BBB may have important implications for the pathogenesis and treatment of cerebrovascular injury during brain trauma. In addition to the barrier functions, which serve to prevent the transport of proteins across the BBB, movement of nutrients, hormones, and drugs across the BBB occurs via carrier-mediated transport. $^{5}$ Thus, transport of substances across the BBB involves barrier and carrier mechanisms. However, few studies have examined both barrier and carrier properties of the BBB during physiological and pathophysiological conditions.

The present studies by Yoshizumi et al attempt to examine barrier and carrier functions of the BBB during ischemia/reperfusion. The authors examined the barrier function of the BBB by measuring the transport of carbon-14-labeled sucrose and the carrier function of the BBB by measuring the transport of iodine-125-labeled 3-iodo-alpha-methyl-L-tyrosine ($^{125}$I-AMT), which has a high affinity toward the large neutral amino acid transport system. The authors found an increase in transport of $^{14}$C-sucrose and $^{125}$I-AMT across the BBB after cerebral ischemia/reperfusion. Thus, periods of ischemia followed by reperfusion affect barrier and carrier properties of the BBB. The present studies of Yoshizumi et al provide new insight with regard to functional changes of the BBB during cerebrovascular trauma.

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A new approach to the integrity of dual blood-brain barrier functions of global ischemic rats. Barrier and carrier functions.
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