Letters to the Editor

Circulating Transforming Growth Factor-β1 Levels in Asymptomatic Carotid Plaques

To the Editor:

It was with great interest we read the report by Cipollone et al. on the role of transforming growth factor-β1 (TGF-β1) in the process of plaque stabilization. The authors demonstrate that TGF-β mRNA levels are increased up to 3-fold in asymptomatic as compared with symptomatic plaques, with a parallel increase in protein expression at immunocytochemistry and Western blot analyses. In addition, TGF-β1 expression was associated with a comparable increase in plaque procollagen and collagen content, thus providing a tangible mechanism of plaque stabilization. As Cipollone et al acknowledge in their discussion, one important issue would be to measure systemic levels of TGF-β1 to verify whether a correlation exist between the localized expression and circulating levels of this cytokine; this correlation would suggest a systemic process in these patients rather than a local phenomenon, and probably might add prognostic information to the management of patients with carotid plaques.

We have only recently completed reviewing the data collected in a 10-year prospective study of the incidence of major cardiovascular events in 42 patients with asymptomatic low-grade carotid stenosis. Patients were consecutively enrolled over a 1-year period from those presenting at the Department of Internal Medicine of the Palermo University Hospital for ultrasound evaluation (high-resolution B-mode ultrasonography using a 7.5-MHz duplex-type probe; Toshiba) of carotid atherosclerotic disease. Specific trials should be designed to directly address the issue of platelet release of TGF-β1 in this clinical setting.

Acknowledgments

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Response:

We read with interest the letter from Ferroni et al about the circulating levels of transforming growth factor-β1 (TGF-β1) in patients with asymptomatic carotid plaques. In fact, in our recent study, we demonstrated that TGF-β1 generated locally within the atherosclerotic plaques is actively involved in the process of plaque stabilization in humans. However, an unresolved issue in this study was whether a correlation exists between the localized expression of TGF-β1 and the circulating levels of this cytokine in high-risk patients.

Starting from this point, Ferroni et al provide 2 important observations in their study. The first is that patients with proved asymptomatic carotid stenosis had markedly higher baseline levels of TGF-β1 compared with control subjects, in whom no lesion could be detected independently of the presence of
cardiovascular risk factors, thus suggesting that systemic TGF-β1 may be associated with the development of atherosclerotic damage. The second observation is that patients with high circulating TGF-β1 levels may experience a higher incidence of hard end point compared with patients with low TGF-β1 levels, thus suggesting a role for systemic TGF-β1 also in the evolution of atherosclerotic plaques developing complications.

Some limitations exist in this study. The first is that the absence of a control group of patients with symptomatic plaques does not permit a complete interpretation of the role of circulating TGF-β1 in the process of atherothrombosis. The second is that the absence of a second measurement of TGF-β1 after the follow-up period does not permit us to know the modifications of circulating TGF-β1 levels during the progression of vessel damage.

Nevertheless, some aspects of the methodology adopted in this study are noteworthy. In particular, the long-term period of observation (8.8 years) permitted to the authors, despite the limited number of studied patients, the observation of a fair number of hard end points and their correlation with the circulating level of TGF-β1. Thus, using this approach, authors observed that TGF-β1 level at enrollment was positively associated with higher incidence of cardiovascular events at 8.8 years of follow-up, thus suggesting the circulating TGF-β1 may predict the risk of future cardiovascular complications in high-risk patients.

Therefore, the evidence rising from the Ferroni study together with our own seems to resolve the question as to whether a correlation exists between the localized expression of TGF-β1 within the plaques and the circulating levels of this cytokine. In fact, TGF-β1 generated from tissue macrophages and smooth muscle cells is an active player involved in the process of plaque stabilization by modulation of the turnover of extracellular matrix. In contrast, circulating TGF-β1 appears to be simply a marker of risk rather than an active mediator. In fact, the results from Ferroni et al on the platelet origin of this mediator, despite being based only on correlative data and indirect observations and therefore fairly speculative, nevertheless identified TGF-β1 as a potential marker of platelet reactivity in humans.

In this light, unfortunately Ferroni et al did not provide any information about the pharmacological treatment of patients, particularly with respect to the antiplatelet therapy. In fact, the recent observations of aspirin-insensitive platelet activity in patients with acute vascular events,2,3,4 probably a consequence of the expression of the aspirin-insensitive cyclooxygenase 2 in young platelets,5,6 seem to suggest that a subgroup of platelets with higher (aspirin-insensitive) reactivity may exist. Whether they are also responsible for the generation of systemic TGF-β1 remains unknown. Thus, further studies using different antiplatelet strategies as a pharmacological tool will be necessary to confirm the role of platelets in the systemic generation of TGF-β1 and to answer the question as to whether TGF-β1 could be the (for a long time searched) marker of the abnormal platelet reactivity responsible for important clinical conditions, such as the so-called “aspirin-resistance phenomenon.”7

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Use of Magnetic Resonance Imaging in Predicting Further Vascular Events Among Patients With Transient Ischemic Attacks

To the Editor:

In the October 2004 issue of Stroke, Purroy et al reported a higher risk of further vascular events among transient ischemic attack (TIA) patients with diffusion-weighted imaging (DWI) acute ischemic lesions.1 They prospectively studied 83 patients with TIA and suggested that duration of symptoms (>60 minutes), presence of DWI acute ischemic lesion, and large vessels disease were important risk factors for the recurrence of vascular events, including cerebrovascular ones.

However, only a minority (9.6%) of patients had their magnetic resonance imaging performed (MRI) within 2 days of symptom onset.1 As quoted by the authors, 10.5% of patients with TIA will have a stroke within the next 90 days of their TIA, and 25% to 50% of these have their stroke within the first 24 to 48 hours.2,3 Therefore, a substantial portion of MRI data may show a second cerebrovascular ischemic event instead of the first stroke/TIA and subsequently do not predict the primary outcome. We would like to know the proportion of clinically defined early/late new vascular events.

Second, the inclusion of TIA as a primary endpoint is problematic and not conventional in relation to stroke prevention trials.4,5 The percentage of patients with TIA versus stroke at outcome should be stated.

Third, a significant proportion of patients presented with vertebrobasilar (43.4%) TIA. What symptoms were accepted as diagnosis of vertebrobasilar TIA? Isolated “dizziness” of unclear origin, for example, is sometimes diagnosed as possible vertebrobasilar TIA but has multiple alternate differential diagnoses that may not ever be conclusively determined. It would have been interesting to know the proportion of vertebrobasilar and carotid TIA among patients with DWI acute ischemic lesions and further vascular events.

Fourth, there are some issues regarding the treatments provided to this cohort that might affect the prognosis of patients. In particular, 54.2% of those enrolled were hypertensive but only 24.1% received antihypertensive medication.6 Furthermore, 15.7% had a severe (>70%) carotid stenosis but only 6% had endarterectomy at discharge. Were these treatments initiated later?

We agree with the conclusion of the authors that MRI may be particularly useful in predicting the future risk of stroke in patients with TIA. MRI should be evaluated with other neuroimaging techniques (transcranial Doppler, etc.) to best-predict those minor strokes and TIAs at risk of new events that would
lead to the identification of a new target population for acute stroke prevention trials.

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Response:  
We thank Boulanger et al for their interest in our article. As they mentioned, we studied 83 patients with transient ischemic attack (TIA), showing that patients with the duration of symptoms lasting for > 1 hour in association with the presence of diffusion-weighted imaging (DWI) acute ischemic lesions and large vessel disease were at highest risk for new cerebral ischemic and any vascular event within the follow-up period (mean of 389 days).1 They raise an interesting point, that is the moment in which DWI study was performed. Ideally, MRI should be obtained as close to the index TIA as possible, to avoid new events being responsible of the brain lesion if any. To limit this issue, we performed DWI acutely (mean of 3 days), and we restricted the inclusion time window for getting the MRI to 7 days after symptoms onset, that was the point from which we considered recurrences and new vascular events. A cluster of TIAs present within 7 days of the index event occurred in 31 cases as stated in Table 2,1 and it was not considered as a recurrence. To avoid that these cases could be a confounding factor, we included the presence of a cluster of TIAs in the logistic regression. It was the presence of DWI lesions but not the presence of multiple TIAs that predicted the risk of recurrence; moreover, those patients had not a higher hazard of having a DWI lesion than patients with a single TIA. In fact, a subset of patients with presumed TIA with a benign short-term course and multiple brief TIAs has been previously described.2 Whether multiples TIAs might induce ischemic tolerance remains to be elucidated.

The commonly quoted risk of stroke within the first 2 days after a TIA varies from 1.4% to 5.5%, depending on the inclusion criteria of different studies.3–6 This means that from a theoretical point of view, in our cohort from 1 to 4 patients might have a stroke within the first 2 days, and a proportion of them might receive the MRI in a delayed fashion. Although this point did not occur in our study, because in every case MRI was done before a new follow-up stroke appeared, it could have happened in a larger sample size cohort and should be taken into account.

Regarding vascular events, as we consider that TIA and cerebral ischemic infarcts share the same underlying pathophysiology, brain ischemia, we include TIA as a primary end point. We understand that studies, such as stroke prevention trials,7–9 that are not entirely conducted by neurologists should take care about TIA inclusion and definitions, but this shouldn’t be a caveat for stroke neurologists.

In fact, the results of our study were similar even when separating cerebral end points into TIA (n = 9) and stroke (n = 7) as suggested by Boulanger et al. Among those TIA patients with a positive DWI, stroke recurrence rate was 15.4% and TIA recurrence rate 14.8%. In contrast, those TIA patients with a negative DWI had lower stroke (7.1%) and TIA (8.9%) recurrence rates. Because sample size is too small for this type of subanalysis, we decided to pool that information in the original article.

According to neurological symptoms, patients were classified in 3 subtypes of TIA: carotid territory in 47 patients (56.6%), vertebrobasilar territory in 15 patients (18.1%), and uncertain territory in the remaining 21 patients (25.3%). We defined vertebrobasilar TIA strictly. We did not consider isolated dizziness, vertigo, drop attack, dysarthria, syncope, or amnesia as symptoms suggestive of vertebrobasilar TIA. The proportion of vertebrobasilar TIA among patients with further vascular events is 40% (6 patients), 27% (13 patients) for carotid TIA, and 4.8% (1 patient) for uncertain territory TIA. The ratio of DWI acute ischemic lesions is also higher in patients with vertebrobasilar TIA, 60% (9 patients), than in patients with carotid TIA, 36.2% (17 patients). Both factors, higher recurrence rate and higher DWI abnormalities among vertebrobasilar TIA, claim in favor of the correct selection of this TIA subtype.

We agree with Boulanger et al that currently available treatments, such as lipid lowering or antihypertensive therapies, are likely to affect the stroke risk. As they pointed out, 54.2% of the cohort was hypertensive, 78.4% of whom received any antihypertensive medication previously. Moreover, 56.7% of the antihypertensive patients (the 24.1% indicated in the article) were given drugs that modulate the renin-angiotensin-aldosterone system. We focused on the study of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blocker because recently their role has been demonstrated in the prevention of recurrent stroke independently of blood pressure reduction.10–12

Regarding large-artery occlusive disease, 13 patients (15.7%) had severe extracranial stenoses, and endarterectomy was performed before discharge in 5 of those cases. In the remaining cases, this treatment was conducted within the following weeks. Although most neurologists believe that in TIA patients, if a high-grade stenosis is identified, an urgent vascular surgery referral is required, some vascular surgeons prefer to delay endarterectomies in the presence of a recent infarction, because they are afraid of bleeding complications. Paradoxically, we believe that some of our TIA patients had a delayed endarterectomy because of the acute lesions in DWI, in spite of being the highest risk patients. Surgeons have to make an effort to better work with this new information close to neurologists.
examination in the hyperacute phase, to identify those at high risk to plan adequate and most aggressive prevention therapies, vascular event recurrence will be reduced.

We agree with Boulanger et al and others that there are areas of important practice variability in the management of TIAs. DWI studies to guide patient care decisions in TIA patients seems promising if our data are confirmed in larger TIA populations. We emphasize that there are some patients, particularly patients with DWI abnormalities associated with long duration of symptoms and large-artery disease, who will benefit from early aggressive therapeutic and preventive strategies.

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Informed Consent for Thrombolytic Therapy in Acute Ischemic Stroke

To the Editor:

We read with interest the article by Rosenbaum et al evaluating how frequently informed consent is documented when thrombolysis for acute ischemic stroke is administered in clinical practice. Through a retrospective analysis of patients who received tissue plasminogen activator (tPA), they found that informed consent was documented in 84% of the charts. As the authors acknowledge, their study is based on current practice immediately after the approval of intravenous tPA for acute ischemic stroke. The authors do not state whether all patients in their study were treated according National Institute of Neurological Disorders and Stroke criteria.

The documentation of consent for standard care surgical procedures may differ from medical interventions. Few physicians will obtain a specific consent for administering intravenous antibiotics for pneumonia. In contrast, all surgeons will obtain a signed informed consent document before operating on a routine herniated lumbar disc. Emergency treatments in which patient incompetence caused by the acute illness or time pressure usually requires a 2-physician consent process. Medical treatments tend to be covered by a general written consent for hospital treatments signed at admission. Moreover, presentation at an emergency ward may itself imply some degree of consent for evaluation and treatment. Differences may also exist by jurisdiction according to local medicolegal practices. Importantly, a clear distinction must be made between consent for research and consent for the standard care. Standards for the former tend to be governed by national or international policy (ie, Declaration of Helsinki), whereas the latter are governed by local jurisprudence.

Thrombolytic treatment of stroke, although a medical therapy, is much more akin to an acute neurosurgical intervention and the low risk of symptomatic intracranial hemorrhage would seem to warrant a documented consent process. Very few patients, in our experience, are competent in the acute phase to make their own decisions about tPA therapy. Although intravenous tPA is considered standard of care for acute ischemic stroke with onset of symptoms within 3 hours, the widening confidence and familiarity with thrombolytic treatment has led to an increasing number of patients being treated outside published guidelines; the same authors showed in a previous article that up to 97% of patients are treated with major or minor protocol deviations (67% are treated in the presence of a major protocol deviation). Off-protocol treatments present the most risk to the patient and medicolegally to the physician.

How many patients in this series were treated outside protocol and how many of them had documentation of informed consent in the chart?

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NINDS Stroke Trial Data Reanalysis Leaves Issues Unresolved

To the Editor:

The reanalysis of the National Institute of Neurological Disorders and Stroke Stroke Trial data1 concludes there is no evidence that the imbalance in baseline stroke severity invalidated the trial results, although the issue of benefit or harm in some subgroups is undecided because of small sample size. A plausible explanation is suggested by the graphed relationship of National Institutes of Health Stroke Scale scores and outcome. Although not concluded as such, the data indicate a nonsignificant treatment effect for the low and high stroke severity groups. The baseline imbalance in stroke severity was most pronounced in these groups, with a lesser imbalance in the intermediate groups. The overall result would not be altered if there were no benefit of treatment in the groups in which there was an imbalance, as the data show.

A previous reanalysis of the NINDS data2 showed the benefit of recombinant tissue plasminogen activator was much reduced toward the end of the 3-hour treatment window. The number needed to treat of 8 for the group overall does not apply to patients treated at that time.

There remains significant uncertainty regarding the benefit of thrombolyis for patients with mild stroke symptoms treated toward the end of the 3-hour period from symptom onset. The reanalysis of data suggests any benefit must be vanishingly small, with the substantial risks of treatment remaining. Further data, not reanalysis, would resolve this issue.

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treatment in patients with acute ischemic stroke who are administered tissue plasminogen activator.

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Strategies in Motor Stroke Rehabilitation

To the Editor:
We read with interest the report by Woldag et al about increased corticomotoneuronal excitability targeting muscles in the paretic hand of chronic stroke patients during voluntary contraction of the healthy hand. The authors interpreted their results as supportive of the concept that use of the unaffected hand may exert a beneficial effect on paretic hand function. We raise your attention to 2 issues that impact on this interpretation. First, measurements of corticomotoneuronal excitability provide mechanistic information on brain activity but do not represent a surrogate marker of paretic hand function. This report carefully describes changes in excitability. In the absence of measures of motor function, it is difficult to assess the functional relevance of these results on neurorehabilitation. For example, voluntary contraction of the healthy hand, as implemented in this study and leading to increased motor excitability targeting the paretic hand, might increase spasticity or elicit other possible detrimental effects on motor control that were not tested.

Second, please note that the increase in excitability targeting the paretic hand of patients was significantly lower than that seen in controls. This decreased ability to facilitate the paretic hand is consistent with a recent report of abnormally high inhibitory drive from the intact to the affected motor cortices in patients with chronic stroke moving the affected hand, which correlated with poor motor performance. Both findings support the alternative interpretation that increased motor activity of the intact hand may not be beneficial to recovery of the paretic hand, a proposal supported by clinical and experimental evidence including: (1) usefulness of intact hand immobilization as adjuvant to paretic hand training during constraint-induced therapy; (2) findings of improved motor function in the paretic hand with anesthesia of the intact hand; and (3) imaging data that demonstrated a negative correlation between magnitude of contralateral activation and functional recovery in patients with chronic stroke.

Clearly, additional work is required to sort out these issues. One attractive approach would be the acknowledgement that mechanisms of recovery after chronic stroke may differ depending on factors like chronicity, lesion size or site, and degree of impairment. If so, apparently contradictory results may be accounted for by heterogeneous patient populations, inclusion criteria, and experimental designs. Future studies should keep in mind apparently conflicting evidence, for example favoring bilateral arm training on one hand and training of only the paretic hand with constraint of the healthy limb on the other, in focused prospective experimental designs that can teach us which patients benefit the most from each intervention. Finally, combining physiological results with direct measures of paretic hand function is likely to provide the highest yield in understanding mechanisms of functional recovery after stroke.

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Response:
The authors of the Letter to the Editor point to the important issue that voluntary activation of the healthy hand in stroke patients may not be beneficial to functional recovery of the paretic hand. The interpretation of the results of our study is in line with this point of view. As we have stated, occupational and physiotherapy must eagerly focus on the paretic hand by using intensive motor practice if there is any voluntary movement of the paretic hand. The main conclusion of our study is that compensatory use of the unaffected hand to achieve the highest possible degree of independence does not exert an inhibitory impact on the excitability of the motor cortex of the affected side. Because it was not the focus of our study, we have never stated that voluntary use of the unaffected hand may have a beneficial effect on paretic hand function. If the message of our paper in this respect was misleading, we are grateful to the authors to make this issue plain.

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Adverse Effects of the Intraluminal Filament Model of Middle Cerebral Artery Occlusion

To the Editor:
Animal models of ischemic stroke are of major importance for experimental stroke research. Comprehensive knowledge of the methodological aspects of the different stroke models available is crucial for data interpretation and correlation to human stroke. We therefore appreciate the recent work of Gerriets et al on complications in different models of focal ischemia in rats,
taking advantage of high-resolution magnetic resonance imaging (MRI) and magnetic resonance angiography.\(^1\)

In addition to their findings of subarachnoid hemorrhage and hypothalamic infarction as a cause of hyperthermia, the appearance of ipsilateral masticatory hyperintensities in early MRI associated with temporal muscle necrosis (Figure) has also been identified recently as a complication of the intraluminal filament model of middle cerebral artery occlusion (MCAO). These lesions resulted in impaired body weight evolution and delayed restoration of neurological function in Wistar rats.\(^2\) This is neither a laboratory-specific nor a rat strain-specific problem, as can be learned from a publication of Palmer et al.\(^3\) Sprague–Dawley rats MRI on day 2 after temporary MCAO (suture technique) depicted extracranial lesions in the temporal muscle that are identical to those found in our laboratory. Unfortunately, the authors do not comment on this finding.

The cause of the masticatory lesions is yet obscure. Although acute ischemic myopathy caused by transection of the external carotid artery had been discussed,\(^2\) further experiments revealed that protection of the external carotid artery was not sufficient to avoid masticatory lesions, and the latter cannot be provoked by transection of the external carotid artery alone (Dittmar MS, Fehm NP, Vatankhah B, unpublished data, 2004). We would be thankful if Gerriets et al could provide information on the presence of masticatory lesions in the rats subjected to MCAO by the 3 different techniques.

We strongly agree on the importance of MRI data in stroke research. Evaluation of different approaches to MCAO in different rat strains by early MRI, not only of intracranial but also of extracranial lesions, is a crucial step to better-understand the pathophysiology of experimental stroke. Ultimately, this may enable us to better-translate animal research into human stroke therapy.

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Response:

Dittmar et al report ipsilateral temporal muscle necrosis as another important source of potential side effects in rat stroke models. This phenomenon occurred in almost half of the animals subjected to middle cerebral artery occlusion (MCAO) and was related to clinical decline.\(^1\) This complication might affect the results of animal stroke studies and thus is of relevance for the transferability of experimental in vivo data to human stroke.

In our recent article, we studied complications and side effects of 3 different rat stroke models: permanent MCAO (suture technique; n = 10), 90-minute transient MCAO (suture technique; n = 10), and permanent MCAO (macrosphere MCAO; n = 10). In this study, male Sprague–Dawley rats (290 to 350 grams) were used.\(^2\) We retrospectively re-evaluated T2-weighted magnetic resonance images that were obtained 24 hours after MCAO for the presence of temporal muscle hyperintensities.

In addition, we retrospectively analyzed T2-weighted images of 30 Wistar rats that were similarly subjected to the 3 aforementioned MCAO techniques (unpublished material). All animals were purchased from Harlan Winkelmann, Borchen, Germany.

No muscle lesions could be detected on MRI (Figure) in Wistar rats (n = 30) or in Sprague–Dawley rats (n = 30).

Although external carotid artery occlusion was performed in a similar fashion in both laboratories (except for the macrosphere MCAO technique, in which the pterygopalatine artery was ligated), some procedural differences can be noticed.\(^1\)–\(^3\) In our laboratory, we do not use electrocoagulation for vessel dissection that potentially might lead to inadvertent tissue damage. Further-

Hyperintense signal changes in T2-weighted MRI of the ipsilateral temporal muscle (arrow) 1 day after surgery for filament MCAO.
more, laser Doppler flowmetry was not applied. This technique requires additional incisions close to the origin of the temporal muscle (or within the muscle) that might lead to impairment of collateral blood flow between the left and right external carotid artery territory.

Furthermore, vendor differences could explain the different results between both laboratories, because we purchase our animals from a different breeder. Rat strain and vendor differences in (intracranial) collateral anastomoses have previously been described, so one can speculate whether this could also apply to extracranial collateralization.4 Further studies are warranted for the understanding of extracranial lesions after MCAO.

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Glucose Metabolism, Noradrenaline Release, and MK-801 in Intracerebral Hemorrhage

To the Editor:

We read with great interest the article by Ardizzone et al1 dealing with the glutamate receptor blockade and glucose metabolism in the experimental intracerebral hemorrhage in rats. The results of their study demonstrated that deoxyglucose uptake was increased in the perihematomal region in rats. In addition, they indicated that the glucose uptake produced by the hemorrhages was blocked by pretreatment of the glutamate receptor antagonists MK-801 and NBQX. The authors proposed that glutamate activation of N-methyl-D-aspartate (NMDA) or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors increased glucose hypermetabolism in perihematomal brain after intracerebral hemorrhage, which may partially contribute to the pathophysiology of this disease.

Several studies have shown the mechanisms for neuroprotective effects of MK-801 in the central nervous system. In a study we presented earlier, changes in noradrenaline (NA) release evoked by L-glutamate was investigated in rat central nervous system.2 In an in vitro study, we showed that L-glutamate increased the release of NA from rat medulla oblongata, and further observed that the facilitative effect of L-glutamate on NA release was more pronounced in spontaneously hypertensive rats than in normotensive rats. In addition, it was demonstrated that MK-801 significantly reserved the increase in NA release evoked by L-glutamate. It might be possible that extracellular glutamate accumulation in the brain after hemorrhage may be attributable to the increased release of NA in the damaged regions. It was already shown that NA might stimulate glycogenolysis, enhance glucose uptake, and increase glucose utilization in the cultured astrocytes.3,4 In this context, it can be speculated that the sympatholytic action might explain, at least in part, the neuroprotective effects of MK-801 in neurotoxic disorders. Therefore, we would like to know the magnitude of the changes in the content or release of catecholamines in the perihematomal brain after intracerebral hemorrhage in the present study of Ardizzone et al. Further studies are necessary to assess more thoroughly the relationships between glucose metabolism and neuroprotective effect of MK-801 in the intracerebral hemorrhage.

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