Letters to the Editor

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Therapy of Early Poststroke Depression With Venlafaxine: Safety, Tolerability, and Efficacy as Determined in an Open, Uncontrolled Clinical Trial

To the Editor:

The development of persistent depressive symptoms is a severe and frequent complication of ischemic or hemorrhagic stroke. The etiology of poststroke depression is not well understood. Only few placebo-controlled, double-blind studies have been carried out, all reporting various degrees of superiority of standard antidepressants over placebos. On the other hand, only few placebo-controlled, double-blind studies have been carried out, all reporting various degrees of superiority of standard antidepressants over placebos.1–2 On the other hand, only few placebo-controlled, double-blind studies have been carried out, all reporting various degrees of superiority of standard antidepressants over placebos.3,4

In most of these studies, patients were examined whose stroke had occurred several weeks to several months before the antidepressive therapy was started. Antidepressive therapy in the first weeks after stroke has not yet been attempted in studies. Drug-induced improvement of neurotransmission, in particular adrenergic transmission, facilitates recovery in animal brain trauma and stroke models.5 Antidepressants enhance neurotransmission by blockade of serotonergic and/or adrenergic reuptake transporters, by blocking the enzymatic degradation of monoamines or by other mechanisms, such as the blockade of presynaptic adrenergic receptors. Therefore, the treatment with antidepressants might in some cases exert a favorable effect on functional recovery independent of the psychopathological state.6

We report data on the safety, tolerability, and efficacy of venlafaxine in patients suffering from acute poststroke depression. Venlafaxine was chosen because of its relatively good tolerability compared with tricyclic antidepressants and because it exerts effects on both adrenergic and serotonergic reuptake transporters.7 Because venlafaxine may increase blood pressure at higher doses,8 particular attention was given to the cardiovascular parameters of blood pressure and heart rate. Patients fulfilled the diagnostic criteria for a major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, on 4 consecutive days, with the exception of the time criterion. We examined 12 patients during a 5-week treatment. Patients had experienced ischemic stroke no longer than 2 weeks before the beginning of the antidepressant therapy. Exclusion criteria were progressive or fluctuating stroke symptomatology, all malignancies, neurological system degeneration, or a history of psychiatric disorders. Patients were administered 75 mg venlafaxine on the first 2 days and 150 mg for the rest of the study period. On the day of the initiation of treatment (day 0) and after 2 weeks and 5 weeks, the depressive symptomatology was measured with the Hamilton Depression Rating Scale (HAM-D; 17 items) and the Montgomery Asberg Depression Rating Scale (MADRS). The European Stroke Scale (ESS) was used to measure the neurological deficit, and the Rankin Scale (RS) and Modified Barthel Rehabilitation Index (MBRI) were used to evaluate the course of rehabilitation. Blood pressure, pulse, and routine laboratory parameters, including liver enzymes, were monitored regularly. ECG was recorded at least 3 times in the course of the treatment.

The mean age of the 6 female and 6 male patients was 66±12 years. Risk factors included diabetes mellitus (n=2), adiposity (n=6), hypertension (n=10), and smoking (n=5). These and additional ailments were treated as clinically indicated. Eleven patients received thromocyte aggregation inhibitors, mostly in combination with low-dose heparin (n=10). One patient was anticoagulated with coumarin.

Venlafaxine was generally well tolerated. One patient with additional chronic hepatitis developed elevated liver enzymes. Dosage had to be reduced to 75 mg/d in 1 case because of agitation. Cardiovascular or hepatic parameters were not systematically affected by the treatment. Three patients suffered from nausea at the beginning of treatment. No other side effects were observed. Drug therapy did not have to be discontinued in any case.

Positive treatment response, defined as a reduction in HAM-D scores of >50%, was observed in 10 of 12 patients after 2 weeks of treatment. Mean±SD HAM-D scores were 24.3±3.2 in the beginning and 7.25±2.3 after 5 weeks of treatment (Figure 1A). Similarly, MADRS scores showed a reduction from 26.7±5.0 to 7.6±2.2 after 5 weeks. Reduction in depression scores were accompanied by significant improvements in scores measuring neurological deficits and rehabilitation: the ESS was 68.3±13.9 on day 0 and 81.4±12.4 after 5 weeks. The RS was 4.25±0.7 on day 0 and 3.0±0.6 after 5 weeks. The MBRI was 35.5±26.6 on day 0 and improved markedly to 82.0±14.3 after 5 weeks (Figure 1B).

This is the first study specifically aimed at the therapy of early depression after stroke. The main finding of this pilot study is that venlafaxine was well tolerated in all 12 patients although patients were elderly, suffered from a recent stroke (<14 days), and had significant other comorbidity. However, the study is limited by its small size, and it cannot be concluded that venlafaxine is an entirely safe drug in stroke patients. Nevertheless, this result differentiates the treatment of poststroke depression with venlafaxine from treatment with tricyclic and other antidepressants, in which side effects often were therapy-limiting.3,4,9 Moreover, the clinical impression was favorable,
although our data do not allow us to give a conclusive statement on the antidepressive efficacy. Without a placebo group there was no adequate control for spontaneous recovery.10

In preclinical models and in patient trials, antidepressant medication has been reported to promote functional recovery after stroke. Because venlafaxine has an effect on serotonin and noradrenaline uptake, one would expect that its positive effect on rehabilitation could be more pronounced than that of selective serotonergic agents, which in animal models under certain circumstances may actually slow recovery.5,6 Again, our data do not allow a definitive clinical statement.

In summary, the most important finding was that no patient had to be withdrawn because of side effects. Double-blind, placebo-controlled, randomized studies comparing the efficacy and side effects of various treatments for the reduction of poststroke depression and the improvement of poststroke recovery, including therapy with antidepressants and psychostimulatory drugs as well as various forms of psychotherapy, are needed. In the meantime, we consider venlafaxine a therapeutic option in selected patients for whom antidepressive medication is needed.

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Poststroke Pruritus

To the Editor:

Although poststroke pain is a well-known phenomenon, poststroke pruritus is a generally under-recognized poststroke symptom. We have found only 10 reported cases of poststroke pruritus in the literature.1,2 We present 2 cases of poststroke pruritus and briefly discuss its etiology and management.

Case 1: A 74-year-old female with a long-standing history of hypertension and hypercholesterolemia developed left-sided pruritus several weeks after a right thalamic stroke. The pruritus was episodic, affecting various localized areas of her left trunk and extremities while sparing the right side. The patient had no history of renal, liver, endocrine, hematologic, or skin diseases, and laboratory findings were unremarkable. Physical examination was significant for an erythematous excoriated area on the left side of the chest. Topical therapy with moisturizers and emollients helped alleviate each episode of pruritus, but the patient continued to have episodic, intense, localized pruritus on various regions of her left side. The patient refused oral medications in order to simplify her medication regimen.

Case 2: A 69-year-old male with a long-standing history of hypertension developed intense pruritus of the left thigh several days after cerebral infarction in the right middle cerebral artery distribution. The pruritus was localized and unrelenting, interfering with sleep. The patient had no history of renal, liver, endocrine, hematologic, or skin diseases, and laboratory findings were unremarkable. Physical examination revealed left-sided hemiplegia and hemiparesis, and an erythematous excoriated left anterior thigh. Treatment with amitriptyline 50 mg a day resulted in resolution of the pruritus within a week.

Although the exact neuroanatomy and neurophysiology of itch perception has not been clarified, it is suggested that itch perception utilizes many of the same neural pathways used in pain sensation.2 Localized pruritus may be a symptom of any focal neurological phenomenon, such as brain tumors,3 multiple sclerosis,4 cerebral vascular aneurysms,5 and peripheral nerve entrapments.6

It is important for physicians caring for stroke patients to be aware of poststroke pruritus and to avoid ignoring the symptoms or pursuing unnecessary work-up for other etiologies. The syndrome consists of excessive localized or generalized pruritus, primarily in the side of the body contralateral to the cerebral lesion. As in poststroke pain, the onset may be from days to weeks after the stroke, and the symptoms respond to medications such as amitriptyline and carbamazepine, although topical emollients may suffice in many cases.1

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Response

This letter emphasizes the poststroke pruritis that can occur in patients with cerebral infarction or hemorrhage. Although not common, we continue to see several cases yearly. Although initially described in capsular infarctions, it also seems to occur in middle cerebral artery distribution vascular lesions as well. When unilateral, contralateral, and poststroke, it is easier to diagnose the cause. Obviously, there are many other causes of pruritis. When it is localized to the lateral thigh, such as in case 2, one must consider other options such as meralgia paresthetica.

I agree that treatment with tricyclics and, more recently, neurontin, can help. Often the symptoms resolve over weeks. Conventional antipruritis treatment, orally or topically, may sometimes help.

Perhaps the greatest challenge is what Latin term to give to this poststroke symptom!

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Mitrail Annulus Calcification and Carotid Atherosclerotic Disease

To the Editor:

In their interesting study, Adler et al1 reported a significantly higher prevalence of carotid stenosis of ≥40% in patients with mitral annulus calcification (MAC) compared with controls. They also stated that whether MAC is a marker or a direct cause of stroke is still unknown.

However, a recently published prospective cohort study2 on the risk of stroke in MAC, with a follow-up ranging from 1 to 6.6 years, showed that the absolute stroke risk was increased in MAC but also that MAC was not an independent risk factor for stroke (HR, 0.76; 95% CI, 0.42 to 1.36). On the other hand, there was a strong independent association of stroke with any carotid stenosis and established risk factors for vascular disease, as expected. These findings suggest that MAC is a marker of generalised vascular disease and not a cause of stroke.

A recently published study3 on 657 patients with MAC and 815 with calcified aortic valve reported strong independent associations of these valve lesions with atherosclerotic risk factors. Although carotid investigation was not relevant in that study, this is a more direct evidence that MAC (and cardiac valve calcification in general)4 should be considered as atherosclerotic comorbidity in stroke and not its cause.

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Response

We are delighted with the interest shown by Dr Boon and colleagues in our study on the association between mitral valve calcification and carotid atherosclerotic disease,1 and we thank them for their insightful comments. Our group has been studying this issue of valve calcification and generalized vascular atherosclerotic disease for several years. In addition to carotid atherosclerotic disease, we have documented with a high association of mitral annulus calcification with aortic atheroma2 and coronary atherosclerotic disease.3

The important work by Boon et al4–6 adds significant data with which we fully agree. This mounting evidence suggests that mitral annulus calcification should likely be considered, in most cases, as an atherosclerotic comorbidity in stroke, and not its cause.

We are currently completing several prospective studies strengthening the hypothesis that mitral annulus calcification is an atherosclerotic process which may be a marker for generalized atherosclerotic vascular disease.

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Rescue Treatment of Acute Parent Vessel Thrombosis With Glycoprotein IIb/IIIa Inhibitor During GDC Coil Embolization

To the Editor:

Endovascular embolization using Guglielmi electrolytically detachable coils (GDC) is a useful technique for treatment of cerebral aneurysms.1,2 Although safe and effective, it carries a
small risk of thrombus formation at the coil mass, with the potential for distal embolization and branch occlusion despite anticoagulation. The risk of thromboembolic complication is approximately 3%,2,3 with a frequency of permanent deficit of 1.7% to 5%.1 Moderate success has been described with fibrinolytic agents,4 though with a risk of aneurysm bleeding. Abciximab is a platelet membrane glycoprotein IIb/IIIa antagonist (ReoPro, Centocor), which inhibits the interaction of activated platelets with the ligand fibrinogen (or fibrin) and has been shown to reduce myocardial infarction and death in patients undergoing coronary intervention.5,6 We present a patient with a basilar apex aneurysm who developed a rapidly progressive thrombus during GDC embolization, which was treated successfully using abciximab.

A 55-year-old woman presented to an outside institution 1 month before admission with intraventricular hemorrhage and ensuing hydrocephalus requiring ventriculoperitoneal shunt placement. On examination, the patient was disoriented and had poor memory and cognition but was otherwise neurologically intact, with normal cranial nerves, speech, and motor/sensory function, and no visual field defects. A CT scan suggested a small clot in the interpeduncular cistern, prompting angiography that revealed a bilobed basilar apex aneurysm measuring 4.9 mm × 5.5 mm. An endovascular approach was undertaken for treatment. The patient was administered 5,000 U heparin, with hourly injections of 2,500 U. After the activated clotting time (ACT) had reached greater than twice baseline, a guide catheter was placed in the left vertebral artery, and the aneurysm was superselectively catheterized with a microcatheter. Two GDC-10 (Target Therapeutics Inc) 5 mm × 15 cm coils were serially deployed and electrolytically detached under high-resolution biplane digital roadmapping. Two additional coils (4 mm × 8 cm, 3 mm × 10 cm) were deployed, after which surveillance angiography revealed a small, nonocclusive thrombus arising from the luminal surface of the coils and projecting into the origin of the left posterior cerebral artery. An ACT immediately obtained was therapeutic at greater than twice baseline level, in accordance with protocol. Serial angiography (Figure) showed marked enlargement of the thrombus resulting in near occlusion of the left P1 segment. Because of thrombus propagation in the context of adequate heparinization, abciximab was considered to decrease platelet aggregation and was administered as a 10-mg bolus followed by steady infusion at 10 μg/min for 12 hours. Repeat angiography performed 5 minutes after administration demonstrated no increase but rather slight decrease in thrombus size, and 30 minutes later complete dissolution with no evidence of distal branch occlusion or embolization. The heparin was allowed to decay after abciximab infusion. The patient recovered from the procedure to her preexistent neurological status and was maintained on abciximab infusion for 12 hours followed by oral daily aspirin (325 mg). She was noted to have no visual field deficits. Conventional and perfusion-weighted MR and CT imaging on postprocedure day 1 showed no evidence of ischemia, infarction, or new hemorrhage. Angiography 2 days later revealed the aneurysm to be well-treated, with no thrombus or distal branch occlusion. The patient was transferred to a rehabilitation facility 2 weeks after admission; she remains neurologically stable at 6 months’ follow-up, and underwent repeat angiography at 6 months that showed complete occlusion of the aneurysm, without coil compaction or recanalization. Both posterior cerebral arteries remain patent and disease-free.

Thromboembolic complications remain a source of morbidity in the endovascular treatment of intracranial aneurysms using coils.1,2 Superselective intra-arterial fibrinolysis using urokinase has been reported in 19 patients having a thromboembolic event during endovascular aneurysm treatment.4 The authors reported complete recanalization in 10 and partial recanalization in 9, with 14 proceeding to a good neurological recovery and 1 patient dying from intracerebral hemorrhage. The advantages of a systematically administered agent such as a GPIIb/IIIa inhibitor are its ability to rapidly attain therapeutic levels within minutes of administration and to potentially obviate the need for superselective microcatheterization of distal branches, with the attendant risk of vessel injury and dissection.

Although the thrombus may have consisted of chronic intra-aneurysmal clot that migrated following coil placement, its rapid progression and subsequent dissolution following abciximab administration argues against this hypothesis. It is likely that the thrombus represented acute platelet activation and aggregation near the microcatheter, coil mass, or in the aneurysm with extension to the aneurysm neck.7 The contribution of the electrolytic detachment mechanism of the GDC system to thrombosis is also unclear. Although the original article by Guglielmi reported a seminal role for electrothrombosis in the therapeutic effect of the coils,8 subsequent evidence to support this in the acute setting is lacking.

In addition to large series showing efficacy when used prophylactically,5,6 abciximab has been used in “rescue” mode during coronary interventions in which new thrombus is observed with >97% success.9 It is, however, associated with a higher risk of vascular access site complications,10 excessive bleeding if emergency surgery is to be performed within 12 hours after administration,11 thrombocytopenia, and intracranial hemorrhage. This entails a potentially significant risk should intragenic aneurysm rupture necessitate emergent ventricular drainage. The inhibitory effects of abciximab on platelet function are observed within 10 minutes of injection.12 Pharmacodynamics of abciximab evaluated by ex vivo platelet flow cytometry suggest that the recovery of platelet function is slow and progressive, with persistent blockade of GPIIb/IIIa receptors of 29% at 8 days after administration, well beyond the circulating lifetime of platelets. This sustained half-life, although desirable in coronary patients, may be dangerous in the neurosurgical population at risk for aneurysm rebleeding. Newer GPIIb/IIIa inhibitors such as the peptide eptifibatide (Integrilin) and the nonpeptide tirofiban (MK-383, Aggrastat), which have shorter half-lives, may be...
safer in patients undergoing endovascular treatment of intracranial aneurysms.

The role of glycoprotein receptor antagonists in the treatment of thromboembolic complications during the endovascular treatment of aneurysms remains undefined and will have to await greater clinical experience. Although the role of abciximab, if any, in the setting of an acutely ruptured aneurysm is unknown, this case suggests that GPIIb/IIIa inhibitors may be helpful in the treatment of progressive recalcitrant thrombolysis in eloquent vascular territory during endovascular therapy.

**Letters to the Editor**

**Spontaneous Stroke in Renovascular Hypertensive Rats**

*To the Editor:*

Zeng and colleagues recently published a potentially important study on the spontaneous stroke in 2-kidney, 2-clp renovascular hypertensive rats. Blood pressure rose to an average of 225 mm Hg 6 weeks postoperatively. Animals displaying neurological symptoms were killed on the third day, and those surviving without neurological symptoms were killed at postoperative week 40. Stroke occurred in 34, including 7 hematomas in 55 animals (61.8%). Microscopic examination revealed fibrinoid necrosis, hyaline degeneration, and hyperplasia of the walls of arterioles and small arteries with or without cell proliferation in the brain. These vascular lesions were not observed in the hypertensive animals without gross brain lesions. I read this paper with great interest, because we published a paper on the cerebral hemorrhage in renovascular hypertensive rabbits over 30 years ago. Despite the species difference, there are many similarities between the 2 studies. I would like to compare the recent study by Zeng and colleagues with our old one and offer some comments.

In our old study, we made rabbits hypertensive by the 2-kidney, 2-clp or 1-kidney, 1-clp procedure. The 2-kidney, 2-clp group was divided into one with moderate narrowing of the renal arteries and the other with a lesser degree of narrowing of the renal arteries, as shown by renograms to specify whether spontaneously occurring death was autopsied for gross and microscopic examination. Most of the deaths occurred within 50 days after renal artery constriction. Animals surviving for a long term were not included in this study. Spontaneous cerebral hemorrhages were found in 31 of a total of 74 spontaneously dead animals (41.9%). There were no significant differences in the incidence of cerebral hemorrhage among the 3 groups. Gross hemorrhages of other organs, including stomach and intestine, were also frequently observed in animals both with and without cerebral hemorrhage. The gross observations indicated that the cerebral hemorrhage developed on the basis of generalized hemorrhagic disorders. Indeed, we later observed prolongation of the clotting time in some of renovascular hypertensive rabbits, and Wiener and colleagues showed evidence for the increased vascular permeability in renovascular hypertensive rabbits. Microscopic examination showed fibrinoid necrosis of arterioles and small arteries of the brain in almost all animals with cerebral hemorrhage and in about half of the animals without cerebral hemorrhage. Also, the vascular lesions were frequently found in the stomach, intestines, and other organs of both animals with or without cerebral hemorrhage. There were dilated small arteries with fibrinoid necrosis in the vicinities of hemorrhagic foci in the brain, giving the appearance of a pseudoaneurysm. Miliary aneurysms of the iris and brain associated with a high risk of cerebral hemorrhage in renal hypertensive rabbits were reported by Santos-Buch and colleagues about 20 years ago.

As in the old and recent studies described, the simple procedure of renal artery constriction was followed by a persistent rise of blood pressure high enough to induce stroke. Both studies indicated that fibrinoid necrosis and related lesions of arterioles and small arteries were the vascular lesions responsible for cerebral hemorrhage. In our study, the vascular lesions were not localized in the brain but instead widely distributed in other organs. Although our article did not refer to the matter, I believe that the generalized vascular lesions were vascular manifestations of the malignant hypertension and the cerebral hemorrhage accompanied by multiple visceral hemorrhages resulted from malignant transformation of renovascular hypertension. It remains unclear whether the renovascular hypertension in rats developed by Zeng and colleagues was malignant or not, because their study lacked gross and microscopic examination of...
organs other than the brain. It may be malignant, because the microphotographs of cerebral arteries illustrated in the article closely resemble those illustrated in our paper, and they appear to be more fulminating than vascular lesions observed in the human brain with hypertensive hemorrhage.

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Response

We appreciate the interest of Dr Fujii in our article describing spontaneous stroke in renovascular hypertensive rats.1 In our study, the systolic blood pressure reached a peak mean value of 215±22 mm Hg at 172±48 days postoperatively in 2-kidney, 2 clip renovascular hypertensive rats (2k2c RHR). Thirty-four of 55 2k2c RHR showed brain lesions including cerebral infarction, hemorrhage, both cerebral infarction and hemorrhage, and subarachnoid hemorrhage after 6 weeks postoperatively, in which the onset time of cerebral hemorrhage was 98±31 days postoperatively in the rats. Similar cerebral hemorrhage was also found in the renovascular hypertensive rabbits in the old study of Ikeda and colleagues.2 Except for the species difference, the main lesion of brain was cerebral hemorrhage that developed on the basis of generalized hemorrhage disorders and occurred within 50 days after renal artery constriction in the rabbits. This kind of brain lesion in the rabbits was more similar to that in 1-kidney, 1-clip renovascular hypertensive rats than that in 2-kidney, 2-clip ones in our study.1

Multiple visceral hemorrhages were not often seen in the 2k2c RHR when they were perfused and killed for histological examination, although the study lacked in gross and microscopic examination of organs other than the brain. But in the other study,3 we found that small coronary arteries in all of the 2k2c RHR displayed medial thickness and cell proliferation of the wall or stenotic lumen without fibrinoid necrosis or atherosclerosis. Multiple myocardial necroses were found in 23 of 55 2k2c RHR. We agree with Dr Fujii that hypertension in some of the 2k2c RHR may be malignant, since the main lesion of cerebral artery in the rats that experienced stroke within 10 weeks after renal artery constriction was fibrinoid necrosis.1 The 2k2c RHR displayed cerebral lesions similar to those found in stroke-prone spontaneously hypertensive rats developed by Okamota and colleagues,4 and some investigators have considered the stroke-prone spontaneously hypertensive rats as experimental models of malignant hypertension.5

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Amphetamine-Facilitated Poststroke Recovery

To the Editor:

The poststroke recovery period represents a largely unexplored potential “window of opportunity” for therapeutic intervention. The studies by Stroemer and colleagues1 represent a significant contribution to our evolving understanding of the neurobiological processes underlying poststroke behavioral recovery and the potential mechanisms by which that recovery may be facilitated by treatment with amphetamine. These findings are of particular interest in view of other laboratory and clinically based reports.

Several lines of evidence suggest that amphetamine’s effect on recovery is at least in part noradrenergically mediated. Pharmacological experiments have shown that centrally-acting α2-adrenergic receptor antagonists increase the rate of motor recovery,2–5 whereas the administration of an α2-adrenergic receptor agonist6–8 or selective α1-adrenergic receptor antagonists are detrimental.3,4 Furthermore, as referenced by Stroemer and colleagues,1 we found that pretreatment with a neurotoxin that depletes central norepinephrine (N-2-chloroethyl)-N-ethyl-2-bromobenzylamine) impairs motor recovery,7 a finding subsequently confirmed by others.8 Consistent with this result, intra-ventricular infusion of norepinephrine mimics the effect of amphetamine.9 The results of these pharmacological studies are supported by experiments in which selective lesions were placed in the pontine nucleus locus coeruleus (LC), the major source of central noradrenergic projection fibers.10,11 In rats, bilateral LC lesions 2 weeks prior to a right sensorimotor cortex lesion resulted in poorer behavioral recoveries when compared with rats that had sham LC lesions.12,13 Unilateral LC lesions, either ipsilateral or contralateral to a sensorimotor cortex lesion, also affect recovery, although the results obtained by individual laboratories vary.12,13

Because LC neurons are highly collateralized,14–16 LC lesioning experiments cannot be used to determine whether noradrenergic regulation of motor recovery after unilateral sensorimotor cortex injury is exerted at the level of the ipsilateral or contralateral cerebral cortex, the ipsilateral or contralateral cerebellum, or other brain structures. We recently reported that a prior selective lesion of noradrenergic projection fibers (dorsal noradrenergic bundle) to the cerebral cortex contralateral, but not ipsilateral, to a subsequent sensorimotor cortex lesion impairs the recovery of locomotor ability.17 This finding is intriguing in view of the earlier18 and present1 observations of Stroemer and colleagues of a significant increase of synaptophysin immunoreactivity in the

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contralateral parietal cortex of amphetamine treated rats. Interestingly, positron emission tomography studies of humans who had recovered motor function after hemiplegic stroke have shown significant increases in regional cerebral blood flow induced by movement of the recovered limb in the sensorimotor cortex contralateral to the injury. \(^1\) Similar changes in the contralateral hemisphere of patients recovering motor function after stroke have now also been demonstrated with functional MRI. \(^2\) – \(^4\) Considered together, these findings suggest that amphetamine may exert its impact on recovery through effects on processes in the contralateral hemisphere. These contralateral effects could also secondarily influence ongoing neuronal reorganization in the hemisphere ipsilateral to the injury.

A pilot clinical study of amphetamine-promoted poststroke motor recovery in humans found that the effect varied among individual patients. \(^5\) Some patients had a dramatic improvement of motor ability, whereas the benefit was only marginal in others. Combining advances in our knowledge of the mechanism of amphetamine- (and noradrenergically) mediated recovery with information obtainable with new neuroimaging technologies may allow the selection of patients who may benefit from these types of interventions in the future.

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Response

The poststroke recovery period has traditionally consisted of symptom management and physical therapy. \(^1\)–\(^3\) Few therapeutic agents have proved successful in improving patient outcome. For example, several pharmacological agents (eg, calcium channel antagonists, excitatory amino acid antagonist) have the potential to reduce ischemic damage \(^4\) – \(^5\) but have problematic side effects and must be applied within minutes of the injury. Thus, not only the treatment strategy but the therapeutic window of efficacy must be considered and must be in a clinically useful window for patient treatment. Most stroke patients do not seek medical help within 6 hours after the onset of clinical symptoms, \(^6\) and thus it is important to pursue therapeutic interventions that are efficacious when administered 24 hours or more after ischemia.

Over the past few years, several pivotal studies have supported the promising use of D-amphetamine treatment in poststroke patients because of both the improved functional recovery \(^1\) and the prolonged therapeutic window of opportunity (several days) available for drug efficacy. \(^7\) – \(^10\) Recent work by our group addresses several possible mechanisms of recovery \(^11\) and improved recovery after D-amphetamine treatment in a rodent neocortical ischemia model. \(^12\) We suggest that multiple mechanisms underlie this treatment, including the amelioration of metabolic depression. Our work proposes a novel mechanism, neuritogenesis and synaptogenesis, as one of several important components in the pathophysiology of improved behavioral response after ischemia and D-amphetamine treatment. \(^12\) Another mechanism of recovery involves D-amphetamine enhancement of noradrenergic-mediated mechanisms, several of which are discussed in the article by Stroemer et al \(^12\) and its accompanying editorial comment by Dennis Feeney. \(^13\) The letter to the editor by Larry Goldstein does an excellent job of further expanding and extending the understanding of the mechanistic basis of D-amphetamine–stimulated, noradrenergically mediated recovery of function after ischemia by discussing several articles that were unable to include our original work by our group because of space limitations. We wish to thank Dr Goldstein for his comments regarding the “significant contribution” of our previous manuscript and for the additional discussion, which we recommend be read in tandem with our article. \(^12\)
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Amphetamine-Facilitated Poststroke Recovery

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