in the synthesis of dopamine, possibly at the level of biotin-dependent tyrosine hydroxylase [5, 6]. In contrast to the suggestion of Wolters and colleagues [1], we would propose that normal PET scans in patients with manganese-induced parkinsonism do not necessarily indicate postsynaptic dopamine deficiency. Particularly in the face of levodopa responsiveness, one can still invoke a disturbance of nigral dopaminergic neurons at a metabolic level before the formation of dopa itself.

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References

Reply
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We agree with Lang and Garnett that the defect in manganese-induced parkinsonism may arise at a stage prior to L-aromatic amino acid decarboxylase. However, we consider that a lesion postsynaptic to the dopaminergic nerve ending is equally possible. The notion that dopaminergic stimulation by the oral route is difficult to sustain. Evidence against this concept is provided by the well-established therapeutic response of the nigral dopamine receptors, with an active half-life of about 65 hours [3]. Cabergoline (Cb) could be a suitable drug to provide continuous dopaminergic stimulation by the oral route. We have treated 18 parkinsonian patients with complex "on-off" fluctuations and disabling dyskinesias with Cb for a mean period of 12.5 months (range 10-18 mo). Cabergoline given once a day was added to levodopa-carbidopa in an open, increasing dose, pilot study. The mean Cb daily dose was 12.2 ± 3.4 mg (range 3-18 mg). The levodopa-carbidopa daily dose was reduced from 1,102.9 mg (baseline) to 691.1 mg after Cb treatment (p < 0.05, Student's t test). The number of "off" hours a day was reduced by 79.2% with respect to the baseline assessment (6.7 hr vs 1.7 hr) (p < 0.01). The score obtained by the Unified Rating Scale for Parkinson's Disease when "off" was also reduced by a mean of 53% (baseline 63.5, after Cb 29.6). "On" dyskinesias were enhanced in duration and severity by at least 50% in 8 patients, and "off" period dyskinesia was abolished in 2, reduced by 50% in 5, and unaltered in 2. Five patients abandoned the study after a mean treatment period of 9.2 months (range 7-11 mo) because of inefficacy (2 patients), increased dystonic dyskinesias (1), severe nausea and vomiting (1), and heart failure (1). These results suggest that Cb, associated with levodopa, has a clear antiparkinsonian effect when given once a day. If the hypothesis that intermittent oral levodopa therapy exerts a deleterious effect on the dopaminergic response can be validated [1, 4, 5], Cb could help to minimize and possibly avoid the therapeutic problems associated with chronic levodopa therapy.

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References
Extracellular Amino Acids in Traumatic Spinal Cord Injury

Anders Lehmann, PhD

Panter and colleagues [1] recently reported on changes in the levels of extracellular amino acids after impact trauma in the spinal cord. My opinion is that the results may be artifactual because of the experimental protocol. In brief, microdialysis probes were implanted into the rabbit spinal cord, and as the authors wished to measure both cations and amino acids in the dialysates, the probes were perfused with distilled water instead of physiological saline. The authors claim that "pilot studies have shown that there are no differences between basal amino acid levels from microdialysis experiments using a distilled water perfusate and those obtained using physiological saline (n = 4)."

The possible importance of amino acids in cerebral osmoregulation has been the subject of at least three independent microdialysis studies [2-4]. These have unambiguously demonstrated that the concentration of certain amino acids depends strictly on the osmolality of the perfusion medium. Taurine is particularly sensitive in this respect and increases when perfusion buffer (NaCl) is decreased by as little as 25 mM [3]. Glutamate, aspartate, and gamma-aminobutyric acid (GABA) are less sensitive but the magnitude of the elevation of the transmitter amino acids is remarkable [2, 3]. For instance, omission of NaCl from the perfusion buffer (which corresponds to a decrease in calculated osmolality from 316.8 to 72.8 mmol/kg) enhances the concentration of glutamate by 15 to 20 times in rat hippocampal microdialysates [2] and by 30 times in microdialysates from the rat dentate gyrus [3]. This response may be submaximal and it could be anticipated that perfusion with distilled water produces even greater effects on glutamate, GABA, and certain other amino acids. There is no reason to believe that the spinal cord differs fundamentally from the hippocampus [2], dentate gyrus [3], or pyriform cortex [4] in response to perfusion with hyposmotic fluid. Likewise, species differences seem very unlikely. Taking into account the perfusion rate and length of the microdialysis probe used by Panter and associates [1], the "basal" concentrations reported are in the range that could be expected during hyposmotic challenge. It is puzzling, though, that the amino acid levels were relatively stable for at least 80 minutes. The statement that steady-state concentrations were reached after only 20 minutes is in sharp contrast to a unanimous literature (for references, see [5]).

The comparison is, however, difficult to make because of the effect of distilled water.

If Panter and associates [1] are able to support their contention in a controlled study, it would be of great interest for those investigating the role of amino acids as osmoregulators in the central nervous system. If not, it means that changes in extracellular amino acids after impact trauma were studied against a grossly abnormal background and consequently need to be reinvestigated.

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References

Reply

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Dr. Lehmann raises the issue of whether osmolarity of the perfusate affects the extracellular levels of amino acids, as determined using microdialysis in uninjured or injured tissue. Recent work by Lehmann and others [1-3] shows that changing the osmolarity of the perfusate during ongoing microdialysis in uninjured tissue can alter the concentrations of certain amino acids, particularly taurine and glutamate.

We have directly compared isotonic (physiological saline) and hypotonic (distilled water) perfusates with regard to basal levels of amino acids in uninjured rat brain. The extracellular levels of only two amino acids were significantly altered by perfusate osmolarity; levels of taurine were increased and glutamine decreased by the use of hypotonic perfusate. All other amino acids (glutamate, aspartate, glycine, serine, threonine, alanine, and gamma-aminobutyric acid) were not statistically different.

We have also compared the use of either isotonic (artificial cerebral spinal fluid) or hypotonic (distilled water) perfusates in experiments examining trauma-related increases in extracellular amino acids in rat brain. Fluid percussion injury to rat brain caused significant increases in the extracellular levels of all excitatory (aspartate and glutamate), inhibitory, and nonneurotransmitter amino acids measured, with no differences in the degree or duration of increase related to osmolarity of the perfusate.

In our original studies, trauma was administered 20 to 30 minutes following insertion of the probe, but we now routinely use a 90-minute waiting period between probe in-