Re: External Carotid Artery Territory Ischemia Impairs Outcome in the Endovascular Filament Model of Middle Cerebral Artery Occlusion in Rats

To the Editor:

We read with interest the article by Dittmar et al1 on body weight loss after middle cerebral artery occlusion (MCAO) by the intraluminal filament method. The authors provided evidence that transection of the external carotid artery (ECA), which is necessary for thread insertion, produced ischemic tissue damage of the lingual and pharyngeal musculature leading to impaired mastication and swallowing functions and eventually loss of body weight. Loss of body weight, however, was also severe in rats subjected to MCAO with no evidence of damage in the ECA territory, suggesting that other factors are involved.

We have investigated whether dehydration, postoperative stress, or altered hormonal secretion contribute to body weight loss after 120 minutes MCAO (Figure).2 Based on plasma osmolality measurements (OSMOL), our rats were not dehydrated, perhaps due in part to the supplemental 0.9% NaCl given to the rats. Corticosterone levels (CORT) were increased only transiently after MCAO, indicating that extensive surgical procedures and postoperative stress do not contribute to weight loss. Unilateral damage to the hypothalamus is typical in MCAO rats and might contribute to postoperative hyperthermia,3 but according to our data this does not affect plasma thyroid-stimulating hormone (TSH). Thus, it is unlikely that thyroid-mediated alterations in cellular metabolic activity account for the loss of body weight. The only long-lasting change, which parallels the loss of body weight (−20%), was a decrease in plasma leptin (LEPTIN). This might be a compensatory response that protects the body from starvation, however, rather than the reason for the body weight loss.

Given that loss of body weight was also severe in rats subjected to MCAO with no evidence of damage in the ECA territory, the minimal postoperative weight loss in sham-operated rats and body weight loss in MCAO models with no surgical manipulation of the ECA,4 the most likely explanation for weight loss in MCAO rats is the extensive corticostriatal damage per se. We agree that there is a need to continue to develop stroke models to provide more accurate and clinically relevant data, but it is also important to ensure the general welfare of experimental animals. The early MRI investigation recommended by Dittmar et al,1 however, is not feasible for large-scale studies. Instead, we recommend (1) careful monitoring of postoperative weight loss, (2) supplemental 0.9% NaCl (intraperitoneally or orally) to avoid dehydration, and (3) availability of liquid food or wet food pellets in home cages to overcome this inescapable complication of the MCAO by the intraluminal method.

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Response: Determinants of Body Weight Changes in the MCAO Filament Model

First of all we would like to thank Drs Virtanen, Sivenius, and Jolkkonen for their inspiring comments on our recent article,1 and we would like to discuss their considerations as far as our work is concerned.

Monitoring of body weight after surgery for intraluminal middle cerebral artery occlusion (MCAO) is an important measure to evaluate the general physiological condition of experimental rats. It is beyond controversy that several causal factors are involved in postoperative weight loss. Obviously, anesthesia and the surgical procedure per se contribute to a graded reduction of body weight, even in sham-operated animals. Primarily, cerebral infarction itself represents the major cause, while the extent of weight loss and the time for regain of baseline levels depend on the duration and severity of ischemia. In our model including 90 minutes MCAO, weight loss was 15% of baseline, and normalization of body weight took 10 days, when the external carotid artery (ECA) territory was not affected. In contrast, Virtanen and colleagues reported a 20% loss of body weight and 28 days for regain of preoperative levels in rats subjected to 120 minutes MCAO. In addition, data obtained from our study demonstrated ischemia of the ECA territory to be associated with a further and prolonged weight loss, which was significantly relevant for functional outcome after stroke.

In the light of these findings, we do not agree that ECA ischemia is just an ancillary complication of the MCAO filament model; we conclude that it endangers model validity and reliability. The variance of poststroke body weight is too large to identify and exclude animals affected by ECA ischemia without the use of in vivo imaging techniques. Furthermore, whether water and food substitution is suitable to overcome differences in body weight changes and other functional parameters caused by ischemic damage to the musculature of the swallowing system has yet to be shown. In addition, since the extent of postoperative weight loss is also a measure of brain damage, the general supply of additional wet food pellets and parenteral liquid may result in

Changes in body weight and plasma measurements after middle cerebral artery occlusion.
a leveling of pathophysiological consequences of more or less severe strokes.

To our opinion, magnetic resonance imaging (MRI) in rats subjected to experimental brain ischemia represents a valuable diagnostic tool, which simultaneously allows noninvasive and serial quantification of both brain damage and, if present, ischemic changes in the ECA territory. In addition, repeated MRI investigations permit long-term morphological examination and thereby a significant reduction of the number of experimental animals. Since rat MRI can be performed using clinical routine scanners, it should be easily accessible at least to research units bound to clinical institutions.

Nevertheless, identifying and excluding rats with ECA ischemia is only second choice. It would be much more appropriate to avoid this complication at all. We therefore recommend 2 strategies: first, screening rat strains other than Wistar for their susceptibility to develop ischemic changes in the territory of the intersected ECA in the context of the intraluminal filament model; second, continued efforts to modify the MCAO filament model in a way that supersedes ECA transection.

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