

## In reply to the letter to the editor

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While the growing interest in the role of oxidative stress and ischemia in the pathogenesis of dementia provides a welcome reprieve from the stale arguments and deafening mantras chanted by the BAPTists and Tauists, I believe we are at a critical phase in which we still have the opportunity to utilize objective scientific methods to further unravel the mechanisms of Alzheimer-type neurodegeneration. First and foremost, in contrast to Dr. Rafael's suggestion, Alzheimer's disease is a genuine entity. Anyone who has seriously studied the disease at both clinical and pathological levels can recognize the classical features and distinguish them from pure cerebrovascular or hypoxic-ischemic injury. Although the clinical manifestations of AD and vascular dementia overlap extensively in the early stages, this does not indicate that the two disease processes are one and the same.

Another important concept that deserves intense investigation is that cerebrovascular injury can contribute to and exacerbate AD-type dementia. By now, there is ample evidence that both disease processes can co-exist in the brain, and therefore are likely to contribute to the cell loss and associated clinical manifestations of dementia. By way of analogy, cirrhosis of the liver can be caused by chronic Hepatitis B virus infection. However, acute or chronic ethanol abuse can also cause liver injury, and each type of exposure can exacerbate liver injury and progression to cirrhosis that is mediated by chronic Hepatitis B virus infection. These are A plus B scenarios.

In our manuscript, we made deliberate efforts to objectively evaluate the consequences of transient hypoxia in relation to AD-type neurodegeneration by evaluating the effects of hypoxic injury on known molecular markers of AD. The study was inspired by recent reports showing cognitive decline in elderly individuals

who had undergone cardio-thoracic surgery. The results of our experiments showed that transient hypoxia was sufficient to trigger a neurodegeneration cascade that is reminiscent of the changes that occur in AD. Although we produced substantial neuronal dysfunction, we did not produce AD. We concluded that transient hypoxia (A) can contribute to the progression of AD (B) in much the same way that acute ethanol toxicity (A) can exacerbate the clinical course of chronic Hepatitis B infection (B) in the liver. However, what we found of particular interest was that the AD-type abnormalities developed after a delay and they were not produced immediately with the insult.

Therefore, an acute insult can result in delayed onset of neurodegeneration.

While we share the interest in determining the potential role of chronic hypoxic-ischemic injury in relation to AD-type dementia, the fact is that acute injury is probably sufficient to do the job, and therefore, it is not necessary to invoke a chronic hypoxic-ischemic hypothesis. The challenge awaiting is to generate an experimental model of chronic hypoperfusion that truly mimics the human condition, i.e. not chronic bilateral ligation of the carotid arteries, and determine the extent to which AD-type molecular abnormalities develop in that setting.

The third message, which is of paramount importance is that, recognizing the potential impact of acute hypoxic or ischemic injury as a co-factor in the pathogenesis of AD-type dementia opens the door for the implementation of prophylactic neuroprotective agents in risky clinical circumstances. Ignoring this principle will likely aid and abet in the projected disastrous growth in the population of demented individuals as is projected for the next several decades. On the other hand, the liberal use of safe and effective neuroprotec-

tion prior to major surgical procedures could represent our first genuine opportunity to intervene and reduce

the incidence and prevalence of AD-type dementia in the coming years.