We thank Drs. Ghanim and Dandona for their comments (1) on our article (2). Their results showing that insulin infusion leads to decreased expression of amyloid precursor protein (APP) and presenilins in human monocytes (3) are in line with reports in cell culture (4) and support the use of insulin in Alzheimer disease (AD) (5). In triple transgenic (3xTg-AD) mice fed with a high-fat diet for 9 months, we have recently shown that an acute insulin injection decreases cortical soluble Aβ40 and Aβ42 back to the level of animals fed with a control diet only 5 min after the injection. To probe the underlying mechanisms, we did find changes in the molecular markers of Aβ production, such as increased α-APP and reduced β-site APP-cleaving enzyme (2), corroborating Ghanim and Dandona’s observation that APP/Aβ production is affected by insulin. However, the half-life of Aβ has been estimated between 1.0 and 2.5 h in an APP mouse model (6). It is thus unlikely that insulin-induced changes in production affect soluble Aβ levels detected in the brain minutes after the injection. The other key mechanism by which cerebral Aβ concentrations are regulated is through brain-blood clearance. Indeed, we found a coinciding increase in plasma Aβ concentrations minutes after the systemic insulin administration (2). Although data directly confirming that insulin triggers a rapid Aβ efflux via the blood-brain barrier are still lacking, higher cerebral blood flow (7) and cerebrospinal fluid Aβ levels (8) have been reported 30 and 120 min after the administration of insulin, respectively. In summary, we agree that the insulin-induced reduction in APP expression and Aβ production is likely to have a major impact in preventing the deleterious effect of a high-fat diet in AD. On the other hand, the rapidity of the drop in cerebral soluble Aβ levels suggests that insulin also directly enhances Aβ efflux through the blood-brain barrier, providing a novel clearance mechanism that deserves further investigations.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References