Hydrogen sulfide (H\textsubscript{2}S) is a water-soluble gas and Tabiano's spa-waters (Italy) are particularly rich in H\textsubscript{2}S (Coruzzi et al., 2010). H\textsubscript{2}S is recognized as an important signaling molecule in various body systems, and accumulating evidence proves that H\textsubscript{2}S donor compounds exert beneficial effects in several animal models of inflammation and ischemia/reperfusion injury (Martelli et al., 2012; Nicholson and Calvert, 2010; Szabo, 2007). Interestingly, brain hydrogen sulfide (H\textsubscript{2}S) synthesis is severely decreased in Alzheimer's disease (AD) patients, and plasma H\textsubscript{2}S levels are negatively correlated with the severity of AD (Eto et al., 2002; Kamoun, 2004; Liu et al., 2008). Here we extensively investigated, therefore, whether treatment with a H\textsubscript{2}S donor and spa-waters rich in H\textsubscript{2}S induces neuroprotection and slows down progression of AD. Studies with sodium hydrosulfide (a H\textsubscript{2}S donor) and Tabiano's spa-water were carried out in three experimental models of AD. Short-term and long-term treatments with sodium hydrosulfide and/or Tabiano's spa-water significantly protected against impairment in learning and memory in rat models of AD induced by brain injection of β-amyloid\textsubscript{1-40} (Aβ) or streptozotocin, and in an AD mouse model harboring human transgenes APP\textsubscript{Swe} PS1\textsubscript{M146V} and tau\textsubscript{P301L} (3xTg-AD mice). The improvement in behavioral performance was associated with hippocampus reduced size of Aβ plaques and preservation of the morphological picture, as found in AD rats. Further, lowered concentration/phosphorylation levels of amyloid/tau cascade proteins were detected in the hippocampus of 3xTg-AD mice treated with spa-water. The excitotoxicity-triggered oxidative and nitrosative stress was counteracted in 3xTg-AD mice, and reduced activity of mitogen-activated protein kinases, which have an established role not only in phosphorylation of tau protein but also in inflammation and apoptosis, was also found. Consistently, modulation of inflammatory and apoptotic cascades also occurred in the hippocampus of 3xTg-AD mice after treatment with Tabiano's spa-water. It seems, therefore, that the neuroprotective effect of H\textsubscript{2}S and spa-waters with high H\textsubscript{2}S content occurs by targeting (directly or indirectly) pathophysiological pathways up- and down-stream of Aβ; interestingly, no signs of toxicity were recorded in the present study throughout the treatment periods. Notably, in our study we started treatment at the initial stage of AD: thus, investigations in AD animals at different stages and ages that reflect the progressive severity of the disease would be worth performing, because clinically relevant. In conclusion, our findings indicate that H\textsubscript{2}S donors and Tabiano's spa-waters successfully target multipleAD-related pathophysiological mechanisms. After sufficient preclinical investigations, appropriate H\textsubscript{2}S supply might represent an innovative approach to slow down AD progression in humans.

References
Szabo (2007). Nat Rev Drug Discov

Keywords: Alzheimer's disease; hydrogen sulfide; neuroprotection
Supported by grant from Fondazione per la ricerca scientifica termale, Roma, Italy.