NEUROCHEMISTRY

NO typical messenger

Nitric oxide (NO) production is implicated in both synaptic plasticity and neurodegeneration in the hippocampus. Unlike other chemical messengers in the brain, NO readily diffuses across cell membranes, so quantifying the effect of endogenous NO has proved difficult. Ledo and colleagues used a sensitive technique to establish that the rates of production and decay of NO vary across the subregions of the hippocampus, which might explain variation in their susceptibility to neurodegeneration.

NO is a highly reactive free radical that has been implicated in excitotoxic processes in various model systems. Activation of NMDA (*N*-methyl-D-aspartate) receptors triggers NO production by neuronal NO synthases. Prolonged activation of hippocampal NMDA receptors — crucial components in the signalling cascades that underlie neuronal plasticity — is associated with neurodegeneration in neurological disorders such as Alzheimer's disease. Knowledge of the concentration dynamics of NO could shed light on its involvement in these physiological and pathological processes.

Ledo *et al.* used NO-selective microsensors to measure the response to stimulation of NMDA receptors in the hippocampus. The authors detected a wide diffusional spread of NO from the point of NMDA receptor activation, but NO signals were transient even when NMDA receptors were stimulated continuously. Although NO was produced in the principal cell layer in all hippocampal subregions, a stronger response was detected in the CA1 region than in area CA3 and the dentate gyrus.

This finding is striking because specific neuronal loss in area CA1 is associated with cognitive decline in Alzheimer's disease. It will now be important to establish the physiological relevance of heterogeneity in the concentration dynamics of NO along the trisynaptic loop of the hippocampus.

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ORIGINAL RESEARCH PAPER Ledo, A. *et al.* Concentration dynamics of nitric oxide in rat hippocampal subregions evoked by stimulation of the NMDA glutamate receptor. *Proc. Natl Acad. Sci. USA* **102**, 17483–17488 (2005)