CHAPTER 13

Possible Anti-Apoptotic Activity of Carnitines on Excitatory Amino Acid-Induced Neurotoxicity

Edoardo Alesse, Grazia Cifone, Adriano Angelucci, Francesca Zazzeroni and Claudio De Simone

INTRODUCTION

Glutamate is the primary excitatory neurotransmitter in the brain. At the neuronal synapse, it interacts with a variety of receptors that specify neurotransmitter interactions and transmit information into target cells. The vast majority of synapses in the central nervous system use glutamate as a neurotransmitter to produce rapid neuronal excitation. Glutamate neurotransmission also participates in neuronal plasticity and neurotoxicity. Neuronal plasticity elicited by glutamate is exemplified by long-term potentiation (LTP) in the hippocampus and long term depression in the cerebellum. However, at supraphysiological concentrations, it is a potent excitotoxin that causes neuronal death through a cascade of cationic and second messenger events. In fact, in many neurologic disorders, injury to neurons may be partly caused by overstimulation of receptors for excitatory amino acids, including glutamate and aspartate. These neurologic conditions range from acute insults such as stroke, hypoglycemia and epilepsy to chronic neurodegenerative diseases such as Huntington’s disease, AIDS-dementia complex, amyotrophic lateral sclerosis, and perhaps Alzheimer’s disease. Furthermore, a plethora of unrelated molecules including HIV gp120, HIV-Tat, tumor necrosis factor (TNF)-α, platelet-activating factor (PAF), interleukin-6 (IL-6), arachidonic acid metabolites, reactive oxygen species and nitric oxide (NO) can trigger neuronal cell death by converging their actions into a common pathway that involves ionotropic glutamate receptors (glutamate-activated ion channels that regulate intracellular Ca2+).
Thus, specific blockers of the NMDA subtype of glutamate receptors, such as MK801 or nemantine, effectively block in vitro the toxic effects of several candidate neurotoxins. These findings suggest that glutamate, besides constituting the direct toxic stimulus in some neurodegenerative diseases, may be a key contributor in some situations, such as HIV-induced neurodegeneration.16

**GLUTAMATE AND CANCER**

Glutamate has been found to inhibit the membrane transport of cystine and to impair the function of macrophages and lymphocytes in vitro.17,18 In patients with advanced colon carcinoma, elevated plasma glutamate concentrations have also been found to quantitatively correlate with reduced lymphocyte reactivity in these persons. After tumor resection, plasma glutamate levels returned to the normal range levels within 1 week of surgery. Concomitantly, a rapid recovery of lymphocyte reactivity toward concanavalin A was observed. Lymphocyte responses against pokeweed mitogen and phytohemoagglutinin, in contrast, remained impaired for at least 6 months, indicating that elevated glutamate levels in patients with colorectal carcinoma are associated with a long-lasting defect in the immune system.13

**GLUTAMATE MAY MEDIATE SOME NEUROLOGICAL DISORDERS**

That glutamate and other amino acids act as neurotoxins was first described in the 1970s, when these agents were given orally to immature animals. Acute neurodegeneration was observed in those areas not well protected by the blood-brain barrier, notably the arcuate nucleus of the hypothalamus. The mechanisms of glutamate-induced neurodegeneration are divergent and activation of all the classes of ionotropic glutamate receptors has been implicated.20

**ISCHEMIC CELL DAMAGE**

Prolonged periods of neuronal tissue anoxia (cardiac arrest, thrombosis) result in ischemic damage and neurotoxicity. Oxygen deprivation leads to a depletion of energy stores, with concomitant acidosis and release of free radicals. Subsequently, the inability of neurons to maintain their resting potential causes membrane depolarization with release of glutamate from presynaptic terminals. The postsynaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) and NMDA (N-methyl-D-aspartate) receptors are then activated by the released glutamate and the $\text{Ca}^{2+}$ concentration increased intracellularly by its entry through the NMDA receptor complex and voltage-sensitive $\text{Ca}^{2+}$ channels.21,22 The intracellular increase of $\text{Ca}^{2+}$ will trigger a cascade of second messengers, many of which