Chapter 12

Proteases and Synaptic Activity

Hiroshi Nakanishi

Laboratory of Oral Aging Science, Faculty of Dental Sciences, Kyushu University, Fukuoka 812-8582, Japan

1. INTRODUCTION

There is growing evidence that the proteolytic machinery has important roles in regulating synaptic activity in the central nervous system (CNS) (Hegde and DiAntonio 2002, Kaczmarek et al 2002; Pawlak and Strickland, 2002; Tomimatsu et al 2002). Under the physiological condition, proteases are tightly regulated to prevent the excessive proteolysis. Their proteolytic activities are regulated by at least three mechanisms: the gene transcription, the activation process of precursor forms, and the interaction with endogenous protease inhibitors. Once proteases are activated, they can exert irreversible cleavage of peptide bonds of various proteins. After cleavage, some substrates are inactivated and others are activated to gain new functions. Under the pathological conditions, activated microglia also release proteases to affect neuronal functions (Nakanishi 2003a, 2003b). Therefore, the precise knowledge about the regulatory mechanism of proteases and their target substrates is critical for the better understanding of their physiological and pathological roles in the CNS. Besides proteolysis, some proteases can also exert their functions by non-proteolytic mechanisms. It is becoming evident that proteolytic cascades have crucial roles in synaptic reactions under the physiological and pathological conditions.
2. TISSUE-TYPE PLASMINOGEN ACTIVATOR (tPA)

tPA is a serine protease that catalyzes the conversion of plasminogen into plasmin, which plays an important role in fibrinolysis. The activity of tPA is regulated by members of the serpine family including protease-nexin 1, neuroserpin and plasminogen activator inhibitor 1 (PAI-1). In the CNS, tPA has been reported to distribute discrete regions of the hippocampus, the hypothalamus, the amygdala and the mehingeal blood vessels (Sappino et al. 1993; Sallés and Strickland, 2002). In the hippocampus, tPA immunoreactivity was found almost exclusively in the mossy fiber pathway. In the amygdala, tPA immunoreactivity was confined to the central and medial amygdala and was almost completely absent in the basal amygdala (Pawlak et al. 2003). These distributions of tPA immunoreactivity correspond well with those of histological zymographic assay for tPA catalytic activity (Sappino et al 1993).

2.1 Plasminogen-Independent Role of tPA in Synaptic Plasticity and Seizure Activity

In 1993, Qian et al identified tPA as a protein encoded by an immediate-early gene, which is induced during seizures, kindling and long-term potentiation (LTP). Since then, much attention has been paid for the function of tPA in synaptic plasticity and seizure activity. Huang et al (1996) utilized tPA-deficient mice to show that the late phase of LTP (L-LTP) in both the Schaffer collateral-CA1 and mossy fiber-CA3 synapses in the hippocampus was significantly impaired. On the other hand, tPA-overexpressing mice show an enhanced synaptic plasticity as evidenced by enhanced L-LTP and an improved performance in a classical protocol of spatial learning (Madani et al 1999). Furthermore, L-LTP in rat hippocampal slices was suppressed by specific inhibitors for tPA and enhanced by an application of tPA (Baranes et al 1998). Although these observations indicate that tPA plays a significant role in neuronal plasticity, the substrates for tPA remain to be determined. One possible substrate is plasminogen that is converted to the broad-spectrum protease plasmin by tPA. However, it has been reported that plasmin-mediated extracellular proteolysis rather impairs the maintenance of LTP by degrading laminin (Nakagami et al 2000). The low-density lipoprotein receptor-related protein (LRP), a cell surface receptor for tPA, is another candidate for tPA substrates. Zhuo et al (2000) have demonstrated that binding of tPA to LRP activates cyclic-AMP-dependent protein kinase (PKA), which plays a key role in L-LTP.