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Protein synthesis inhibition and memory: Formation vs amnesia ☆

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Abstract

Studies using protein synthesis inhibitors have provided key support for the prevalent view that memory formation requires the initiation of protein synthesis as a primary element of the molecular biology of memory. However, many other interpretations of the amnesia data have received far less attention. These include: (a) protein synthesis may play a constitutive role in memory formation, providing proteins prior to an experience that can be activated by training; (b) protein synthesis may be needed to replace proteins available prior to learning but 'consumed' by learning; (c) inhibition of protein synthesis impairs the well-being of neurons, leading to an inability to deliver resources needed for memory formation; and (d) inhibition of protein synthesis results in abnormal neural functions that interfere with memory. One of these, abnormal release of neurotransmitters after inhibition of protein synthesis, is detailed here, along with a review of many circumstances in which it appears that protein synthesis at the time of training is not required for the formation of new memories.

Evidence of activation of cell signaling molecules and transcription factors is another form of support for a role of training-initiated protein synthesis in memory. However, recent findings suggest that many of these molecules are activated by training and remain activated for days after training, i.e. activated for times well beyond those typically invoked for memory consolidation processes. Reviewing these results, this paper suggests that the long-lasting molecular changes may be the basis of a form of intracellular memory, one responsible for up-regulating the probability that a neuron, once activated in this manner, will engage in future plasticity. This view melds ideas of modulation of memory with those of consolidation of memory.

Keywords: Anisomycin; Memory consolidation; Memory modulation; Memory; Molecular bases

1. Introduction

Many reports begin with a well-accepted statement that there are at least two stages of memory. As generally proposed, memory is maintained soon after experience, by a short-lived temporary process that is dependent on modifications of existing proteins (e.g., Kandel & Schwartz, 1982). As this memory mechanism decays, mechanisms responsible for permanent memory storage supplant the temporary process. These mechanisms are generally believed to be dependent on new protein synthesis and to form the basis for cellular memory consolidation at a cellular level (Dudai, 2002; Kandel, 2001; Squire, 1987).

Of several ways in which new protein synthesis may be important to memory (Glassman, 1969), one is the commonly held view that new protein synthesis is needed for the modifications of neuron–neuron functional connectivity. Many of the studies that discuss protein synthesis-dependent memory do so on the basis of findings that protein synthesis inhibitors impair memory, identifying results obtained with the inhibitors as demonstrating a requirement for protein synthesis in memory consolidation. However, other interpretations of these findings are less often considered (Gold, 2006). One is that intact protein synthesis is necessary in a more constitutive manner for replenishment of materials used in memory formation

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(Routtenberg & Rekart, 2005). Another possibility is that protein synthesis is needed for maintenance of cell health at a level that can sustain the use of cellular resources to fine-tune the connectivity of the nervous system in response to memory (Rudy, Biedenkapp, Moineau, & Bolding, 2006). Yet another interpretation is that inhibition of protein synthesis results in abnormal neural functions that interfere with memory, a possibility supported by recent evidence from the author's laboratory (Canal, Chang, & Gold, 2007) as described below.

The present paper examines several classes of findings that are not readily incorporated into the view that new protein synthesis is a necessary component of the mechanisms by which new memories are formed. Although this review will mainly focus on contemporary studies, it is important to note extensive evidence from the 1970s and 1980s that led many investigators to conclude that the evidence did not support the idea that protein synthesis was necessary for memory formation, that the effects of protein synthesis inhibitors on memory were very complex, and that the results supported many alternative explanations (e.g., Barraco & Stettner, 1976; Cooper, Bloom, & Roth, 1978; Martinez, Jensen, & McGaugh, 1981). These points of view were the motivation for the review by Davis and Squire (1984), in which they defended the idea that protein synthesis was necessary for memory. Importantly, whatever conclusion one now draws about this issue, it is not the case that these early studies led to a consensus that protein synthesis was necessary for memory. Nonetheless, statements espousing this view have become standard in the introductions to and rationales for studies of protein synthesis and memory.

2. Is protein synthesis necessary for memory and synaptic plasticity?

2.1. Examples of plasticity resistant to inhibition of protein synthesis

2.1.1. Memory

Although protein synthesis inhibitors often impair memory across species and tasks, it is also the case, as noted by Routtenberg and Rekart (2005), that intact memories are sometimes formed even in the presence of extensive inhibition of protein synthesis. Specific behavioral variables appear to be important. For example, amnesia is attenuated in graded manner by increasing the number of training trials or by increasing the intertrial interval (Flood, Bennett, Orme, & Rosenzweig, 1975; Quartermain & Botwinick, 1975), or by increasing the intensity of a training footshock (Flood, Bennett, Orme, Rosenzweig, & Jarvik, 1978a). Thus, views regarding the requirement of new protein synthesis for memory formation do not comprehensively incorporate a significant amount of the available data. Results like these, particularly when viewed together with the pharmacological 'rescue' studies described later, indicate that protein synthesis is not universally necessary for the formation of memories, specifically including long-lasting memories.

2.1.2. LTP

The multiple variables involved in memory research might confuse the interpretations in favor of or against a role for new protein synthesis in memory. In recent years, many reports have noted that protein synthesis inhibitors have effects on long-term potentiation (LTP) that are analogous to those seen in many memory experiments, specifically intact early LTP with rapid decay in rats and mice treated with protein synthesis inhibitors. However, like memory, LTP is sometimes insensitive to inhibition of protein synthesis and, as in memory experiments, there are specific variables that seem to determine the sensitivity or resistance of LTP to protein synthesis inhibitors. In rat visual cortex, theta burst stimulation resulted in a slowly developing LTP that was blocked by protein synthesis inhibitors and a rapidly established form of LTP that was not blocked by the inhibitors (Kurotani, Higashi, Inokawa, & Toyama, 1996).

Although not directly involving inhibition of protein synthesis, a more recent paper (Steward, Huang, & Guzowski, 2007) provides additional evidence that protein synthesis may not always be necessary for LTP. Perforant path LTP was established in rats using either 250 or 400 Hz stimulation trains. Although the expression of LTP was comparable under these conditions, important molecular markers of LTP induction were very different. LTP induced with 400 Hz tetanizing stimulation trains was accompanied by increased c-Fos and MAP kinase expression. However, LTP induced with 250 Hz trains did not engage these molecular mechanisms. Importantly, the magnitude of LTP was similar under both stimulation conditions, suggesting that there may be at least some forms of synaptic plasticity that do not require new protein synthesis.

A recent report (Fonseca, Vabulas, Hartl, Bonhoeffer, & Nagerl, 2006a) provides additional evidence that protein synthesis is not necessary for LTP. The findings of this report suggest that protein synthesis and degradation must be in balance in order for the production of LTP in CA1 (Fonseca et al., 2006a). As reported by many others, late-LTP was impaired in the presence of protein synthesis inhibition. In addition, the report showed that late-LTP was also impaired by pharmacological inhibition of proteasome-mediated protein degradation. Of particular relevance to the present discussion was the finding that simultaneous inhibition of both protein synthesis and degradation did not interfere with the induction and maintenance of LTP. Regardless of the specific interpretation regarding balance of synthesis and degradation, the findings indicate clearly that establishment and maintenance of LTP can occur in the absence of protein synthesis. The ability of pharmacological inhibition of protein degradation to rescue LTP adds to other examples noted below in which drugs can rescue LTP from the effects of protein