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STRESS-INDUCED METAPLASTICITY: FROM SYNAPSES TO BEHAVIOR

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Abstract—Synaptic plasticity, specifically long-term potentiation and long-term depression, is thought to be the underlying cellular mechanism for learning and memory processes in the brain. About two decades ago a new concept was introduced, namely metaplasticity, which comprises changes that modify the properties of synaptic plasticity due to a priming or preconditioning event. While metaplasticity was initially defined and studied predominantly on a synaptic and cellular level, it soon became apparent that the term could also be very useful to describe plasticity changes on a more global level, including environmental stressors as priming events and altered behavior as outcome measures. We consider here whether it is helpful to conceptualize these latter effects as ''behavioral metaplasticity'', and in which sense this view fits into the original concept of metaplasticity. By integrating the literature on environmental effects on plasticity, especially stress, plus developmental aspects as well as genetic and epigenetic modifications, we shape the framework in which the term ''behavioral metaplasticity'' should be considered and discuss research directions that can help to unravel the mechanisms involved in both synaptic and behavioral metaplasticity.

Key words: metaplasticity, stress, synaptic plasticity, cognition, LTP.

Contents

METAPLASTICITY – THE EMERGENCE OF A CONCEPT

Metaplasticity is a term that was coined by Abraham and Bear (1996) to encompass a variety of phenomena, all characterized by a sensitivity of long-term potentiation (LTP) and long-term depression (LTD) to the recent history of prior neural activity. This was put simply as the ''plasticity of synaptic plasticity''. There are two key elements to this conceptualization: (1) the changes that occur modify the properties of synaptic plasticity in some way, e.g., the direction, degree or persistence of the plasticity, and (2) there is a period of time between the initial neural activity (sometimes referred to as ''priming'' or ''preconditioning'') that induces the metaplasticity and the subsequent induction of the synaptic plasticity. The persistence aspect of metaplasticity reflects that a new kind of plasticity, different from LTP and LTD, has been imposed. Metaplasticity is often referred to as a ''state'' change in the cells or synapses that leads to different LTP/LTD outcomes than would otherwise occur.

Apart from the two defined elements of metaplasticity, the authors were inclined to be inclusive in terms of what phenomena would fall under its rubric. In particular, they entertained the idea that the priming activity could take various forms, ranging from activity (or inactivity) at the synapses for which LTP/LTD were to be induced, to more widespread activity of the cells or network in which the synapses of interest were embedded. Most of the

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Abbreviations: BLA, basolateral amygdala; CBP, CREB binding protein; CREB, cyclic AMP-responsive element binding factor; DG, dentate gyrus; Dnmt, DNA methyl transferase; GR, glucocorticoid receptor; HAT, histone acetyltransferase; HDACs, histone deacetylases; LTD, long-term depression; LTP, long-term potentiation; MeCP2, methyl cytosine-binding protein 2; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; NFκB, nuclear factor kappa B.

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early studies specifically approached metaplasticity from the first perspective, focusing on local circuitry (i.e., synapse-specific to cell-wide alterations). However, perhaps because of the stated desire for inclusivity, the term metaplasticity has subsequently expanded to include changes in LTP/LTD following more global signals, such as hormone release. Stress hormones such as corticosterone have featured particularly strongly in this regard (Kim and Yoon, 1998). Thus, prior delivery of corticosterone *in vivo* or *in vitro* can up- or down-regulate LTP depending on the synapses under study and the timing of the events, and these effects can be replicated by substituting behavioral stress for the hormone administration (Foy et al., 1987; Shors et al., 1989; Diamond et al., 1992; Pavlides et al., 1993, 1996; Shors and Dryver, 1994; Bramham et al., 1998; Kim and Diamond, 2002; Kavushansky and Richter-Levin, 2006; Kavushansky et al., 2006).

One of the key issues for the metaplasticity field now is whether metaplasticity occurs *in vivo* in a way that is relevant to behavioral phenomena such as learning and memory (Hulme et al., 2013). This is very similar to the question of behavioral significance that is faced by the synaptic plasticity field itself for LTP and LTD. The finding that stress can induce a metaplastic state was a significant step forward in signaling metaplasticity as a behaviorally relevant phenomenon. This has been supported by extensive studies in the visual cortex and elsewhere demonstrating changes in LTP and LTD capability following periods of altered sensory experience, such as altered visual experience or enriched environment exposure (Kirkwood et al., 1996; Duffy et al., 2001; Philpot et al., 2003; Irvine et al., 2006). Thus, it appears that metaplasticity can be induced regardless of whether priming is by some specific neurophysiological/neuroendocrine manipulation, or by some relevant sensory/behavioral manipulation. The mechanisms mediating metaplasticity may vary in each case, but importantly the expression of the metaplasticity is through altered synaptic plasticity. However, the shift from local circuit manipulations to behavioral manipulations challenges the assumption that synaptic metaplasticity is indeed at the heart of the resulting alterations to induce plasticity. It is thus not clear, for instance, whether stress-induced inhibition of LTP and the enhancement of LTD in the hippocampus are mediated via the same metaplastic mechanisms which mediate synaptic metaplasticity in its original form.

In the present article, we will consider the question of whether it is helpful to conceptualize a second broad sub-family of metaplasticity effects, namely ‘‘behavioral metaplasticity’’. Here, the expression of the metaplasticity is altered learning and memory. The mechanism of this alteration could in principle be due to altered synaptic plasticity capability, but other mechanisms could be more important, for example reorganization of network connectivity, altered network excitability leading to altered throughput, or epigenetics. As an extreme example, experiences early in life can lead to dramatic changes in learning much later in adulthood. Is this metaplasticity? We will review such phenomena and consider for which ones the term ‘‘behavioral metaplasticity’’ may prove to be a useful concept, without damaging or violating the fundamental principles of metaplasticity per se.

STRESS EFFECTS ON NEURAL PLASTICITY

LTP and LTD are widely regarded as the two main forms of synaptic plasticity in the brain underlying memory processes (Bliss and Lomo, 1973; Bliss and Collingridge, 1993). In general, it was intensively reported that acute stress and the resulting elevation of circulating corticosterone level profoundly influence the capacity for long-term synaptic plasticity in limbic structures, such as the hippocampal formation. In the CA1 region of the hippocampus, acute stress impairs LTP and primed-burst potentiation, a low threshold form of LTP, *in vitro* (Foy et al., 1987; Shors et al., 1989; Mesches et al., 1999) and *in vivo* (Diamond and Rose, 1994; Xu et al., 1997; Maroun and Richter-Levin, 2003). Additionally, acute stress also enhances LTD in the hippocampus *in vitro* (Kim et al., 1996; Yang et al., 2005) and *in vivo* (Xu et al., 1997). These effects on synaptic plasticity occur following a number of stressors including administration of shock (Shors et al., 1989), exposure to a novel environment (Xu et al., 1997), placement on an elevated platform (Xu et al., 1998; Maroun and Richter-Levin, 2003), or exposure to a predator (Mesches et al., 1999). In an important study, Shors and her colleagues demonstrated that the LTP deficits following stress only occur in rats unable to terminate (or control) their exposure to shock (Shors et al., 1989). Thus, it appears that the effects of the stressor on synaptic plasticity are determined not just by the physical facets of the stressor, but also by its psychological impact (Kim et al., 2006), suggesting the involvement of effects on a large scale network of interactions (Segal, 2010).

These profound suppressive effects of stress on plasticity in the hippocampal formation are suggested to result from the dense distribution of corticosterone receptors found in this region (Sapolsky, 1993; McEwen, 1999). The hippocampal formation is highly enriched with the two types of adrenal steroid receptors (Reul and De Kloet, 1985). Mineralocorticoid (Type I) receptors (MRs) have a high affinity for glucocorticoids and are generally saturated under basal conditions whereas glucocorticoid (Type II) receptors (GRs) have a 10-fold lower affinity for glucocorticoids and are only occupied when circulating levels of glucocorticoids are elevated, such as during periods of stress (Reul and De Kloet, 1985). Similar to the effects of stress on synaptic models, initial studies reported that the administration of high doses of corticosterone either *in vivo* or *in vitro* (Diamond et al., 1992; Pavlides et al., 1996; Alfarez et al., 2002) resulted in similar effects on plasticity. It was tempting to speculate that the effects of stress depend on elevated levels of adrenal hormones in the hippocampus. This line of thought regarding corticosterone, stress and hippocampal metaplasticity