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Studying synaptic plasticity in the human brain and opportunities for drug discovery

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Synaptic plasticity is the ability of synaptic connections between neurons to be strengthened or weakened; a process that is central to the information processing within the brain and which plays a particularly important role in enabling higher cognitive processes [1,2]. Its role in disease is becoming increasingly clear across a wide spectrum of CNS disorders. Thus, for example, dysfunctional synaptic plasticity has been reported in neurodegenerative disorders such as Alzheimer's Disease (AD) as well as in schizophrenia and in a range of disorders associated with learning disabilities [3]. Moreover, maladaptive plasticity processes in response to specific external challenges are believed to underlie disorders such as addiction and post-traumatic stress disorder (PTSD). The molecular basis of normal and disease plasticity is rapidly being unravelled such that synaptic plasticity now provides a unique platform from which to launch the hunt for highly innovative drugs to treat CNS disease by either, firstly, rectifying identifiable abnormalities in these processes, or secondly, utilizing these processes as a vehicle to rectify, or bypass, other mechanisms underlying disease. In this respect, recent advances have been made in studying synaptic plasticity in humans at the molecular through to clinical level and these approaches now provide a real opportunity to test synaptic plasticity as a treatment paradigm for a wide variety of CNS disorders.

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Synaptic plasticity and its role in CNS disease

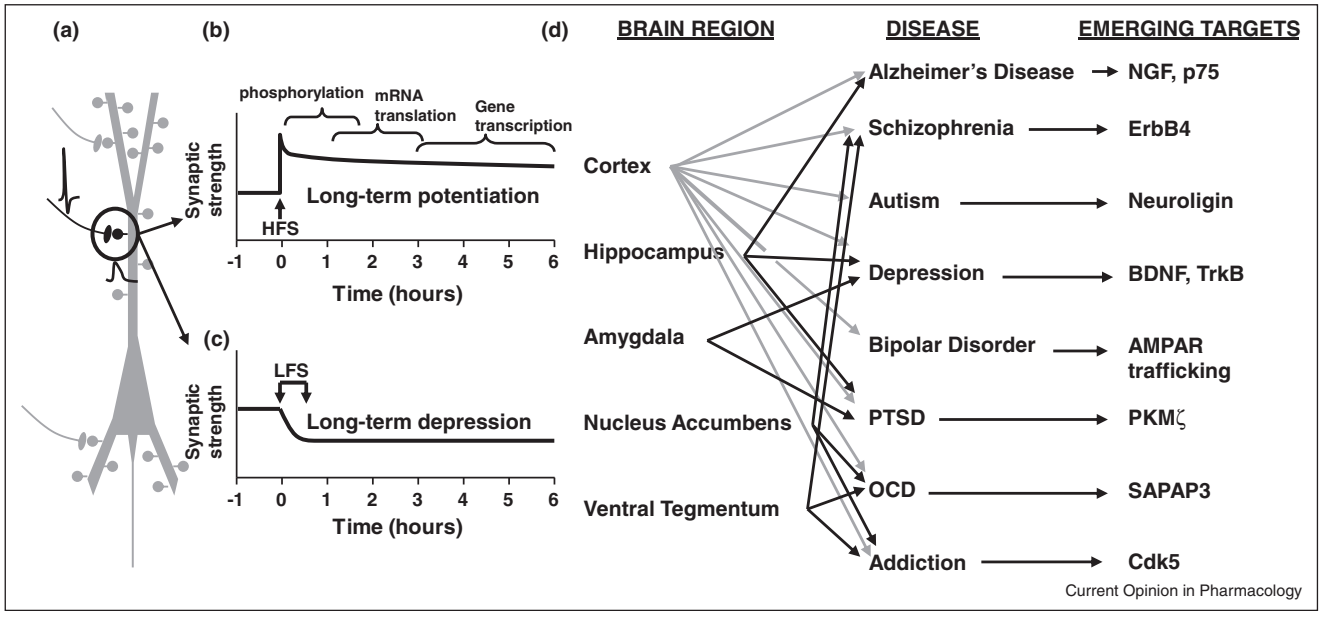
Synaptic plasticity provides the nervous system with the capacity to modify its organization and structure to adapt to alterations in its environment due, for example, to changes in sensory, pathological or drug challenge. It can be manifest as:

1. *Activity-dependent functional plasticity*, a collective term for a family of mechanistically diverse phenomena (e.g. paired-pulse facilitation/depression, long-term potentiation/depression (LTP/LTD)) that permit patterned afferent activity or correlated afferent and postsynaptic activity to exert short (milliseconds to seconds) or long-lasting (hours to months) bidirectional control of synaptic strength without overt remodelling of the synapse.
2. *Activity-dependent structural changes* which include the generation of new neurons and the formation or splitting of synaptic connections or the pruning of pre-existing ones that are believed to be initiated by many of the same mechanisms that mediate activity-dependent plasticity.
3. *Activity-dependent changes in neuronal excitability outwith the synapse itself* which include changes in voltage-dependent conductances involved in dendritic integration or axonal conduction.

The magnitude, direction, probability of induction and persistence of each phenomenon are highly dependent upon the pattern of afferent input that initiates it. Low-frequency (<2 Hz) afferent input generally induces depression, whereas high frequency (>5 Hz) generally induces potentiation of synaptic strength. Thus, synaptic plasticity is closely linked to neuronal network dynamics and its functional role within the CNS is largely governed by the neural circuits within which it occurs, for example, cognition in frontal–striatal–thalamic circuits, fear in amygdala-based circuits, reward/hedonic state in mesotelencephalic projections and related circuits, mood in prefrontal cortex and limbic structures and pain in spinal cord and descending rostral ventromedial medulla-spinal projections. In this respect, there is a growing opinion that therapy based on neuronal plasticity should be able to modify disease set points which are untouched by existing pharmacological treatments and specifically rectify aberrations in sensory, emotive, and contextual systems that underlie many CNS disorders (Figure 1) [4].

Taking addiction as an example, drugs of abuse elicit strong memories and are powerful reinforcers that can lead to long-lasting pathological behaviors characterized

Figure 1



Basic features of synaptic plasticity and the potential for targeting plasticity in a range of disease areas. **(a)** Diagram illustrating synapse specific plasticity whereby afferent activity (illustrated by spike) produces postsynaptic potentials (shown below highlighted synapse) which can then be independently modulated depending on the pattern of afferent activity. **(b)** High frequency afferent activity results in long-term potentiation (LTP) which occurs in a series of temporal phases ranging from early modification of existing synaptic proteins (e.g. phosphorylation) through to transcriptional and translational-dependent late phases. **(c)** In contrast, low-frequency afferent activity results in a long-term depression (LTD) of the synaptic response. **(d)** Synaptic plasticity is a general feature of the CNS but aberrant plasticity particularly in brain regions is associated with a range of specific disease states. These may represent mechanistically distinct features and provide the opportunity to develop targeted therapeutic strategies based on discrete signaling pathways. *Abbreviations*: HFS, high frequency (afferent) stimulation; LFS, low-frequency stimulation; PTSD, post-traumatic stress disorder; OCD, obsessive compulsive disorder; NGF, Nerve growth factor; p75, neurotrophin receptor; ErbB4, Erythroblastic leukemia viral oncogene homolog 4; BDNF, Brain derived neurotrophic factor; TrkB; Tyrosine kinase receptor B; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; PKM; Protein kinase Mζ; SAPAP3, SAP90/PSD95-associated protein 3; Cdk5, Cyclin-dependent kinase 5.

by high rates of relapse caused by cue-induced or stress-induced craving. Recent work has established that drugs of abuse hijack synaptic plasticity mechanisms in specific reward\hedonic circuits, including the mesolimbic dopamine system [5]. As such, substantial therapeutic benefit should be provided by preventing or reversing this 'hyperplasticity'. The reversibility or extinction of 'hyperplasticity' is also receiving attention in disorders such as post-traumatic stress disorder (PTSD) and other anxiety disorders where pathological memory processes and maladaptive synaptic plasticity in fear-related and anxiety-related circuits occur. 'Hyperplasticity' is also a feature of pain. Thus, agents (e.g. formalin and capsaicin) that produce peripheral inflammation induce synaptic potentiation at C-fiber-lamina 1 projection neuron synapses [6] whereas analgesic opiates (e.g. remifentanyl) induce a synaptic depression, and following withdrawal produce a rebound potentiation that correlates with the magnitude of withdrawal-induced hyperalgesia. Furthermore, patterns of afferent nerve stimulation that induce LTP or LTD in rats produce hyperalgesia or hypoalgesia, respectively, in human subjects [7]. Thus, within the pain field there is a growing belief that synaptic plasticity at nociceptive synapses is a key signal amplifier in pain pathways responsible for central sensitization [8,9] and is a potential target for the treatment of chronic pain states [10]. The converse phenomenon 'hypoplasticity' also manifests as disease as exemplified in schizophrenia where NMDA receptor hypofunction has been demonstrated in postmortem human brain tissue and reduced LTP has been observed in a rTMS study in schizophrenic patients [11]; abnormalities that are believed to be central to the psychotic and impaired cognitive aspects that are characteristic of this disorder.

Mechanisms underlying synaptic plasticity

It is important to realize that the phenomenological terms used to describe synaptic plasticity represent umbrella terms for multiple forms of potentiation and depression. Thus, each form of plasticity can rely on distinct molecular mechanisms in, firstly, different brain regions (e.g. LTP, a process induced during learning [12••], is mechanistically different in the hippocampus than in the amygdala), secondly, different neuronal populations in the same brain region (e.g. endocannabinoid and nonendocannabinoid-mediated LTD in medium spiny, indirect and direct pathway projection neurons from the striatum to the basal ganglia, respectively [13••]), or thirdly, even