It’s All about the Memories

Imagine a heroin addict. This young man started heroin when he was 18, and took drugs for the next 10 years. He was caught by the police, arrested, convicted, and spent half a year in prison. While there, he went through withdrawal. Afterward, he began to feel better, gained weight, and felt like a new man. He decided he was through with drugs. When he was released from prison, he went back home. While approaching the same subway stop where he’d previously experienced heroin withdrawal symptoms (while trying to score more heroin), he began to sweat and gag. After getting off the subway, he vomited on the tracks. He alleviated these symptoms by injecting heroin. The next day, he experienced intense craving and withdrawal symptoms, and again relieved them by injecting heroin. This cycle repeated itself over the next days, and he was soon re-addicted (O’Brien, 1976). So, why did this person experience withdrawal symptoms at the subway stop when he had been clean and sober for 6 months?

The answer lies in the complex interactions of glutamate in the brain. Glutamate is the most common excitatory neurotransmitter in the vertebrate brain. Our neurons’ synapses have the ability to reorganize their structure, function, and connections, a characteristic known as “synaptic plasticity.” The connections among neurons are fundamental to the development, maintenance, and remodeling of complex neural circuits. Glutamate is a key player in producing and maintaining these changes in the synapse. It does this by either increasing or decreasing the strength (receptor density) – becoming stronger with long-term potentiation (LTP) and becoming weaker with long-term depression (LTD). With LTP, individual synapses become stronger and form neural networks. It is these neural networks that create learning and memory – a process important in the craving and relapse of drug addiction.

To understand this process, let’s look more closely at the synapse and glutamate. All neurotransmitters can have different types of receptors. Glutamate and the other excitatory amino acids have at least four different types of receptors. Three of these are ionotropic receptors where the binding of glutamate to the receptor causes an ion channel to open on the dendrite of the neuron. This is a relatively quick open-and-close event. The most important of these ionotropic receptors are the NMDA (N-methyl-D-aspartate) and AMPA (a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors. Both NMDA and AMPA receptors are involved in regulating the synapse plasticity via long-term potentiation (LTP). How does this happen?

NMDA receptors have two important characteristics: They are highly permeable to Ca2+ ions and they have a voltage-dependent block by extracellular Mg2+ ions. So, only a significant depolarization – such as that caused by the activation of AMPA type glutamate receptors – will unblock the Mg2+ and allow Ca2+ to flow through the NMDA receptor channels. This Ca2+ influx can trigger a number of intracellular processes, among them the up-regulation of AMPA receptors (Patterson, 2011; Nikolaev, 2012). LTP involves the insertion of AMPA receptors at the synaptic membrane. LTD involves removing AMPA receptors from the synapse. The NMDA receptor number remains relatively constant, so it is the ratio of AMPA to NMDA receptors at the synapse that produces LTP or LTD (Lee, 2012). As the dendritic membrane acquires more AMPA receptors, it enlarges. Small dendritic spines are the preferential sites for LTD induction. These small spines have a small number of AMPA receptors – so there’s room for growth. Large spines have large numbers of AMPA receptors, and it’s thought that these larger spines act as memory units. Matsuzaki (2004) found that these larger spines are more stable and are resistant to long-term potentiation, which is critical for memory storage. Thus, in the large spines, memory storage is protected by its resistance to long-term potentiation. The LTP caused by an increase in the AMPA:NMDA receptor ratio is believed to be the basis for a number of behavioral effects, such as the craving and relapse produced by addictive drugs.

Glutamate can also bind to a metabotropic receptor. Metabotropic receptors are both slower and longer acting than ionotropic receptors, for they activate a second messenger cascade system that can result in the opening of ion channels located elsewhere on the same postsynaptic membrane. The biochemical cascades caused by these metabotropic receptors can change the cells’ responsiveness to neurotransmitters by making them more or less likely to respond to neurotransmitters. Research has identified eight different subtypes of metabotropic glutamate receptors, which are grouped into three families. Group I of these metabotropic glutamate receptors (which modulate the NMDA receptors) are thought to be the neurological basis for autism and Fragile X (Chen, 2012). The Group II family of metabotropic receptors regulates the release of glutamate in neurons that project from the prefrontal cortex and amygdala to the nucleus accumbens, the “pleasure” center of the brain. It is this pathway that is strengthened via LTD in drug addiction and is important in the relapse in drug-addicted individuals.

The strong pairing between the young man’s former use of heroin and all the environmental cues associated with his drug use – the sights, the sounds, the smells of the subway terminal – created a strong memory, initiated by LTP and thought to be stored as large dendritic spines. This “addiction memory” (von der Goltz, 2009) was later activated by these self-same environmental cues, producing a craving and withdrawal that caused him to relapse.
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References