Disrupting drug related memories for relapse prevention: challenges for translation

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As is now well documented, fully consolidated memories can, under some circumstances, become labile – or destabilised - at retrieval and must undergo a restabilisation process to persist in the brain. This 'reconsolidation' can be disrupted leading to amnesia. In the case of memories established by the association of discrete conditioned stimuli in the environment (CSs) with self-administered addictive drugs such as cocaine, heroin and alcohol, disruption of reconsolidation leads to the future loss or reduction in the capacity of these CSs to support instrumental drug seeking and decreases their ability to precipitate relapse. In experimental animals, knockdown of the immediate-early gene zif268, protein synthesis inhibition or interference with intra-cellular signaling pathways in the basolateral amygdala, as well as blocking neurotransmission events using NMDA receptor or ß-receptor antagonist treatments given systemically or into amygdala, when given in association with CS presentation at retrieval, prevent drug memory reconsolidation. The same is true for conditioned fear memories. Extinction of drug CSs (i.e. repeated non-reinforced CS presentations) can also decrease their capacity subsequently to support drug seeking and relapse, but this tends to be context specific and to be less long-lasting in its effects – unless it is preceded by a brief memory reactivation, when so-called 'super-extinction' can occur whereby the CS loses its conditioned reinforcing and other pavlovian properties to influence drug seeking and relapse in the longer term.

However, there have been failures to see reconsolidation blockade and super-extinction effects in some animal studies and this presents a challenge when considering translation to the clinic. Part of the explanation concerns clear definition and identification of markers of memory destabilization. Retrieval under some circumstances does not apparently result in destabilization and thus no reconsolidation process follows, making the memory resistant to manipulation by amnestic agents. Even under quantitatively controllable experimental conditions, the degree of CS presentation that results in memory destabilization-reconsolidation is difficult to specify. Similarly the boundary between memory reactivation (to induce reconsolidation) and extinction, which follows greater numbers of CS presentations is also relatively unspecified. Many treatments that prevent reconsolidation will also prevent extinction – but the behavioural outcomes are opposite: thus, if a treatment designed to prevent reconsolidation is instead given in association with 'too many' CS presentations (that initiate extinction), then the drug-CS memory will persist, and not be weakened. Similarly, if a treatment (such as D-cycloserine) is given to enhance extinction, but there are insufficient CS presentations to initiate extinction, the memory will be strengthened, increasing the subsequent likelihood of CS-induced relapse.

While reconsolidation blockade and super-extinction have been used successfully in the clinical treatment of phobias (i.e. fear memories), with hints of effectiveness in PTSD, there are few examples of successful reconsolidation or super-extinction-based anti-relapse treatments for drug addiction. I will discuss that this largely stems from the difficulty in employing retrieval conditions that destabilize the memory limiting the potential of reconsolidation (and extinction) based treatments for addiction. But the potential of such treatments will great if a better basic understanding of the underlying molecular and psychological processes can be achieved.