Plenary lectures

How abused drugs interact with learning and memory systems?

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One of the most intriguing functions of the brain is the ability to store information provided by experience and to retrieve much of it at will. Learning is the name given to the process by which new information is acquired by the nervous system and is observable through changes in behavior. Memory refers to the encoding, storage, and retrieval of learned information. There are at least three definable neural systems in the brain for processing and storing information that are influenced by drug abuse, dependence and addiction [White and McDonald, Neurobiol Learn Mem, 2002].

A neural system that includes the amygdala mediates stimulus-reinforced learning. This process includes conditioned incentive learning of both skeletal responses (i.e., observable approach or escape behavior) and internal active states (i.e., unobservable patterns of autonomic and central responses that can be perceived as rewarding or aversive).

A different neural system, in which the matrix compartment of the caudate-putamen is the main structure, mediates stimulus-response associations that are expressed in behavior as habit learning. Habits are well-learned sequences of behavior that are elicited automatically by the appropriate stimuli. Thus, this form of learning promotes repetition of behaviors performed in the presence of drug-related stimuli.

The third neural system that includes the hippocampus mediates stimulus-stimulus learning (i.e., declarative or cognitive learning). In contrast to conditioned incentive and habit learning, declarative learning does not include information about responses or any particular behavior. Instead, this system unifies knowledge of relationships between external events relevant to the situation in which a drug is obtained (e.g., the social situation). There is also evidence that this system can acquire information about relationships among external cues and internal unconditioned and conditioned affective states. Once this type of information has been acquired by the hippocampus, the modulating action of some drugs might increase the tendency for the system to recall contextually relevant information as well as the incidence of drug-related cognitions and behavior.

Finally, there is a substantial convergence of both the molecular pathways and the neural circuits associated with learning and memory and with drug addiction. Both processes are modulated by the same neurotrophic factors, share certain intracellular signaling cascades, depend on activation of the transcription factor cAMP response element-binding protein (CREB) and are associated with similar adaptations in the formation or loss of dendritic spines. Moreover, the long-lived neural changes that underpin addictive behavior are becoming clearer thanks to knowledge gleaned from the learning and memory field. Thus, the importance of learning and memory in drug abuse has made understanding of these phenomena one of the major challenges of modern neuroscience, a challenge that has only begun to be met.

Therapeutic intervention in HIV-1-induced disruption of the blood brain barrier

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The blood-brain barrier (BBB) is the critical structure for preventing HIV-1 trafficking into the brain. Specific HIV-1 proteins, such as Tat protein, can contribute to the dysfunction of tight junctions at the BBB and HIV-1 entry into the brain. Tat is released by HIV-1 infected cells and can interact with a variety of cell surface receptors activating several signal transduction pathways, including those localized in caveolae. Our studies focused on the mechanisms of Tat-induced caveolae-associated signaling at the level of the BBB. Treatment with Tat activated the Ras pathway in human brain microvascular endothelial cells (HBMEC). However, caveolin-1 silencing markedly attenuated these effects. Because the integrity of the brain endothelium is regulated by intercellular tight junctions, these structural elements of the BBB were also evaluated in the present study. Exposure to Tat diminished the expression of several tight junction proteins, namely, occludin, zonula occludens (ZO)-1, and ZO-2 in the caveolar fraction of HBMEC. These effects were effectively protected by pharmacological inhibition of the Ras signaling and by silencing of caveolin-1. In addition to Ras, the Rho cascades of small GTPases (RhoA, Rac1 and Cdc42) have also gained considerable recognition as powerful regulators of actin cytoskeletal organization and integrity of the BBB. Treatment with Tat markedly increased membrane RhoA and GTP-RhoA levels in HBMEC, while the total level of RhoA was not changed. Most interestingly, Tat induced a decrease in claudin-5 expression by a Rho-dependent mechanism. Indeed, inhibition of the Rho signaling by the C3 exoenzyme blocked Tat-induced disruption of claudin-5 expression in human BMEC. Tat-induced stimulation of the Ras and Rho pathways may also induce inflammatory responses. Indeed, treatment of HBMEC with Tat resulted in a significant up-regulation of E-selectin, CCL-2, and IL-6 promoter activities and protein levels. In addition, E-selectin promoter activity was markedly up-regulated in HBMEC co-cultured with HIV-1-infected Jurkat T cells. Simvastatin, the HMG-CoA reductase inhibitor, effectively blocked proinflammatory reactions induced by Tat and HIV-1-infected Jurkat cells. Similar protective effects were exerted by overexpression of PPAR-α or PPAR-γ in HBMEC as well as pretreatment of HBMEC with selective PPAR agonists. The present results indicate the importance of caveolae-associated signaling in the disruption of tight junctions upon Tat exposure. They also demonstrate that caveolin-1 and PPARs may constitute critical modulators that control signaling pathways leading to the disruption of tight junction proteins. Statins, such as simvastatin, may have beneficial effects in reducing the inflammatory responses at the level of the blood-brain barrier in HIV-1-infected patients.

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