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Some of the characteristics of schizophrenia may be understood from the point of view of excessive incentive learning (IL). IL is the acquisition by previously neutral stimuli of an increased ability to elicit approach and other responses. Dopamine (DA) plays a key role in the establishment and maintenance of IL. DA D1-like or D2 receptor antagonists block the acquisition of IL. In animals that have already acquired IL, acquisition-blocking doses of these drugs do not initially block expression; with continued testing whereas in the drug state, IL gradually is lost. D3 receptor antagonists appear to have a different profile, blocking expression of IL at doses that fail to block acquisition. Thus, the D3 partial agonist BP 897 blocked expression but not establishment of conditioned activity or place preference based on amphetamine. BP 897 or the selective D3 receptor antagonist SB-277011A attenuated conditioned suppression of lever pressing produced by a stimulus previously paired with electric shock but failed to block establishment of conditioning when given during stimulus-shock pairings. The selective D3 receptor antagonist ABT-127 blocked expression of conditioned activity based on cocaine at a dose that failed to block acquisition. These effects were doubly dissociated from those of the D2-preferring antagonist haloperidol that blocked acquisition at a dose that failed to block expression. A number of signaling molecules including PKA, ERK1/2, p38, protein kinase C and calcineurin in the nucleus accumbens have been implicated in IL. DA may produce IL by modifying glutamatergic z-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. How D1 and D2 receptors interact to produce this learning remains to be worked out. Results suggest a complex interaction of DA, acting at a number of its receptor subtypes, with glutamatergic synapses mediated by cascades of signaling molecules to produce and maintain IL. A better understanding of these mechanisms will point the way towards the development of new pharmacological tools for the treatment of schizophrenia (funded by NSERC).

**SYMPOSIUM 2: FORWARD AND REVERSE GENETIC APPROACHES TO REWARD AND ADDICTION, COMBINED WITH: GENETICS IN DRUG ADDICTION**

**S4 MICROARRAY STUDIES ON DRUG-INDUCED CHANGES IN GENE EXPRESSION**

M.J. Kreek

Abstract not provided