Neurobiology and pharmacology of psychostimulants

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Psychostimulants share with highly palatable food the property of increasing dopamine (DA) transmission preferentially in the nucleus accumbens shell. A critical role of this property for the acquisition of reinforcing effects by cocaine is indicated by local silencing of D1 DA receptor expression with siRNA engineered lentivirus (Lecca et al, in preparation). Activation of DA transmission by food reward undergoes rapid habituation in the accumbens shell but not in the core or in the prefrontal cortex. These adaptive properties of food-induced stimulation of DA-release in the shell are consistent with a role of shell DA in incentive learning, i.e., in the acquisition of incentive properties by reward predictive stimuli. Activation of accumbens shell DA by psychostimulants and drugs of abuse in general does not undergo habituation. It has been suggested that resistance to habituation of the ability of drugs of abuse to preferentially stimulate DA transmission in the NAc shell results in abnormal strengthening of stimulus-drug associations and acquisition of excessive motivational properties by discrete stimuli or contexts predictive of drug availability and this abnormal incentive learning process has been suggested to constitute the first stage of drug addiction (Di Chiara, 1998 and 2002). Stimuli conditioned (CSs) by predictive association with drugs of abuse are thought to play an important role in the acquisition, maintenance and relapse of drug dependence and DA might be involved in these actions. Drug-CSs differentially activate DA as compared to food-CSs in the NAc shell and core. Thus, while drug-CSs stimulate DA transmission in the NAc shell but not in the NAc core (Bassareo et al. 2007), the opposite applies to food CSs, as these stimuli activate DA in the NAc core but not in the shell (Bassareo et al, in press). Both drug- and food CSs, however, activate DA transmission in the prefrontic/infralimbic cortex. These observations might be incorporated into an incentive learning theory of drug addiction. Thus, while the ability of drugs of abuse to releasing DA in the NAc shell in a non-habituating fashion, by abnormally facilitating learning of drug-conditioned incentives, would be instrumental to initiate drug seeking, drug-conditioned incentives, by releasing DA in the NAc shell would facilitate the further acquisition of secondary incentives, thus inducing the formation of a chain of CSs that ultimately induce and maintain compulsive drug seeking. The fundamental contribution of individual, mainly genetic, risk factors to this mechanism is consistent with genetic epidemiological investigations in humans and is modeled by studies in psychogenetically selected rat lines (Piras et al, in preparation). This theory might be extended to explain disturbances of food seeking, such as compulsive overeating, as the result of the existence, in certain individuals, of an abnormality in the DA-stimulant properties of food CSs, namely, the property to release DA in the NAc shell (Di Chiara, Dopamine in disturbances of food and drug motivated behavior: a case of homology, Physiol& Behav, 2005).