

NEUROTRANSMITTERS AND RECEPTORS AS THE TARGETS FOR ADDICTION TREATMENT: A SHORT REVIEW

B. SRINIVASA REDDY^{1*}, M. SATHISH KUMAR¹, N. V. RAMA RAO¹, A. NARENDRA BABU¹, N. RAMA RAO¹, J. MANJUNATHAN²

¹Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur, ²CAS in Botany, University of Madras, Guindy Campus, Chennai.
Email: bsrpharmacy80@gmail.com, jmanjunathan@gmail.com

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ABSTRACT

Addiction is an important health problem which is characterized by a chronic relapsing disease with implications in social and economic life. Addiction research begins with the neurotransmitters and their mechanisms by which drugs acts and shows their effects. In this review we have presented an overview to summarize the role of neurotransmitters in addiction like Dopamine, Glutamate, Noradrenaline and Serotonin. Mesocorticolimbic dopamine system plays a crucial role in the mechanism responsible for the rewarding effects. All neurotransmitter levels in the addiction are based on the stimulant and inhibitory actions of the drugs. Receptors are the major targets for the neurotransmitters and drugs to show their actions. Drugs target the muscarinic and nicotinic receptors, which play a major role in the psycho stimulant addiction on the behavioral effects. Drugs which are having addiction properties are due to alterations in the intracellular pathway and also expression of gene products upon signaling.

Keywords: Addiction, Relapsing disease, Neurotransmitters, Receptors, Mesocorticolimbic system.

INTRODUCTION

According to International Classification of Diseases (ICD-10) Addiction is defined as the dependence syndrome as being a cluster of physiological, behavioral, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviors that once had greater value.

In 1964 a WHO Expert Committee introduced the term 'dependence' to replace the terms 'addiction' and 'habituation'. The term can be used generally with reference to the whole range of psychoactive drugs (drug dependence, chemical dependence, substance use dependence), or with specific reference to a particular drug or class of drugs (e.g. alcohol dependence, opioid dependence). While ICD-10 describes dependence in terms applicable across drug classes, there are differences in the characteristic dependence symptoms for different drugs.

Neuroplasticity is the brain's ability to reorganize itself by forming new neural connections throughout life. Neuroplasticity allows the neurons (nerve cells) in the brain to compensate for injury and disease and to adjust their activities in response to new situations or to changes in their environment.

Role of Neurotransmitters in Addiction

Dopamine

Dopamine (DA) is an excitatory neurotransmitter mainly present in the central nervous system. DA receptors have subtypes they are mainly two families D1 (D1, D5) and D2 (D2, D3, D4) families, which are classified based on the pharmacological action. Activation of D1-family receptors increases cyclic adenosine 3', 5'-monophosphate (cAMP) through stimulation of adenylatecyclase via Gs stimulatory G-proteins. But activation of D2-family receptors decreases cAMP through Gi (inhibitory) pathway. The cAMP is formed from the ATP through an enzyme adenylatecyclase (AC) and it is metabolized by enzyme phosphodiesterase (PDE) which is present in the cytoplasm. Intracellular cAMP activates the kinase enzymes like protein kinase A (PKA) and G-protein receptor kinase3 (GRK3). PKA phosphorylates receptors and channels, and activates important transcription factors like cyclic adenosine monophosphate response-element binding protein (CREB) [1-3]. Drugs which are having addiction properties are due to alterations in the intracellular pathway and also expression of gene products upon signaling. Some examples include brain-derived neurotrophic factor, cyclin dependent kinase5, nuclear factor kappa-B, GluR1 (AMPA glutamate

receptor sub-type-1), among others, implicated in drug-induced neuroplasticity[4, 7].

Endogenous DA levels are increased in the VTA, NAc, OFC and thalamus when the stimulant substances are used such as nicotine, cocaine and methamphetamine[8] and also these stimulant drugs associated with reward system there by increases the release dopamine intensively compared normal reward system. Reward system of DA in the brain includes the VTA and NAc, where sequence of reaction occurs based on the drug stimuli and behavior, i.e., drug-seeking consumption. These drugs stimulation causes increased extracellular DA firing to initiate craving [9]. In drug-dependent subjects, craving is correlated with the amount DA release [10]. Subsequently, craving is hypothesized to be due to neuro adaptations of the mesolimbic DA system [11, 12]. Furthermore, the DA system is implicated in attentional bias towards drug-related stimuli and also DA system is associated with the development and storage of memory [13].

Mesocorticolimbic Circuitry

It is a drug substrate for Dopaminergic cell bodies in the VTA and their projections to the NAc and PFC, and GLU projections from the PFC to both the VTA and NAc, generally define the fundamental circuitry of the Mesocorticolimbic reward system. Other important brain structures associated with motivational memories and drug taking and dependence include the amygdala, hippocampus and hypothalamus [14]. Although other Neurotransmitter systems are clearly involved, studies strongly support that activation of them Mesocorticolimbic system is key to the Reinforcing effects produced by drug in humans [15].

Dopamine and Glutamate

Cellular mechanisms in addiction involving dopamine, glutamate, and their intracellular and genomic targets have been the focused in both the areas of reward-related learning and addiction. These two neurotransmitter systems, widely distributed in many regions of cortex, limbic system, and basal ganglia, appear to play a key integrative role in motivation, learning, and memory. It is currently believed that coordinated molecular signaling of dopaminergic and coordinated molecular signaling of dopaminergic and glutamatergic systems, particularly through dopamine-1 D-1 and glutamate N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, is a critical event in the induction of intracellular transcriptional and translational cascades, leading to adaptive changes in gene

expression and synaptic plasticity, the reconfiguring of neural networks, and ultimately behavior [16,17,18,19].

Synaptic proteins are synthesized by the gene expression and the gene is expressed when the Phosphorylated CREB (cyclic adenosine monophosphate response-element binding protein) is binding to numerous response elements in many genes (such as c-fos, c-jun, NGFI-B, homer1A, ania3, arc, and zif268 (NGFI-A, krox-24)). CREB is acting through the calcium and PKA pathway, this CREB in corticostriatal region plays a major role in detection of coincidence and learning, this process is transduced by the glutamate and dopamine signals, respectively [20]. Phosphorylations of many intracellular proteins are majorly by the enzyme protein phosphatase-1 (pp-1) [21]. Induction of synaptic plasticity is mainly genes and transcription factors. Corticostriatal region have abundant genes and transcription factors. Genes which are responsible for the generation and phosphorylation of CREB is dependent on NMDA and/or Dopamine D-1 dependent. Drugs which are antagonize the NMDA and/or Dopamine D-1 actions they inhibit the generation of CREB [22, 23, 24, 25, 26, and 27]. Although how these mechanisms translate into stable synaptic change and alter atoning behavior remains unknown.

Noradrenalin

Noradrenalin has more stimulant activity to increase in dopamine and it regulates the dopamine transmission in the mesocorticolimbic circuit. Cell bodies of the noradrenalin projected at the nucleus accumbance and ventral tegmental area (VTA) from brain stem A1 and A2 areas as well as locus ceruleus (LC) [28]. Noradrenalin acts through the excitatory mechanisms and these projections directly stimulate the dopamine cell firing and indirectly noradrenergic neurons projecting to the prefrontal cortex (PFC) affect the dopamine neurotransmission in the nucleus accumbance [29].

Serotonin

5-HT (Serotonin) is also play a role in brain reward system. Neurotransmission is mediated by the 5-HT receptors, till now 14 different 5-HT receptor subtypes are identified. Among these 5-HT_{1B} involved in reward system, 5-HT_{1B} receptors are strongly expressed in mesocorticolimbic system [30]. Release of 5-HT is regulated by the auto receptors present in the nerve endings [31] and hetero receptors located on dopaminergic, glutamatergic, GABA-ergic or cholinergic neurons [32].

Muscarnic receptor

Substantia nigra and ventral tegmental area (VTA) have the dopaminergic projections these projections represent the pathway for the natural reward system, drug reward system and these projections made by dopamine p-containing neurons. Muscarnic receptor M1, M2, M3, M4, are identified and newly M5 receptors mRNA are also identified. mRNA of the muscarnic receptor present in dopamine p-containing neurons. Heroin addiction is treated by the scopolamine, i.e., non selectivity of muscarnic receptor.

Nicotinic Receptor

The brain contains different neurotransmitter systems, such as DAergic, serotonergic, GABAergic and glutamatergic system. In addition, an extensive network of connections is modulated by acetylcholine (ACh): the cholinergic system. The receptors of the cholinergic system are divided into muscarnic acetylcholine receptors (mAChRs) and nicotinic acetylcholine receptors (nAChRs). Because varenicline has a strong affinity to the nAChRs and not to the mAChRs, we focus on the nicotinic receptor subtype to assess the potential role of varenicline in the treatment of drug dependence. Nicotinic AChRs are ionotropic; they form ion-channels in the plasma membrane of the cell that can be opened by ACh and nicotine (Itier and Bertrand, 2001) [33]. Nicotinic AChRs include 5 subunits, formed by combinations of α -subunits ($\alpha 2$ - $\alpha 10$) and β -subunits ($\beta 2$ - $\beta 4$). Combinations result in receptors with different neuronal distribution and affinity regarding ligand binding [34]. The $\alpha 4\beta 2$ nAChR consists of two $\alpha 4$ - and three $\beta 2$ -subunits combined to a neuronal nicotinic receptor with high affinity for nicotine, which is widely distributed and represented in the rat brain [35] and stably expressed in the human brain [36]. The subgroup of $\alpha 7$ nAChRs is

widely present in the human central nervous system. They are found in the cortex, hippocampus, VTA, and striatum, where they are expressed both pre- and post-synaptically on cholinergic neurons as well as on glutamate- and GABA neurons [37, 38].

Nicotinic AChRs seem to be centrally involved in the neuroadaptations induced by exogenous nicotine, amphetamine and cocaine. For example, repeated nicotine exposure results in an increase in functional nAChRs and, more specifically, sensitization of the mesolimbic DA response to nicotine [39]. In addition, Schoffelmeeer et al. showed that endogenous release of DA following amphetamine and cocaine administration and subsequent nAChR activation is a precondition for increased DA release in the NcA and behavioral sensitization. Thus, nAChR activation may be crucial for the development of dependence to many drugs of abuse [40].

Nicotine and the dopaminergic system

One third of the $\alpha 4\beta 2$ nAChRs are located on DAergic cell bodies in the mesostriatal DA system [41, 42]. Subsequently, nicotine enhances DA release through presynaptic nAChRs in striatal synapses and is thus characteristic for reward-related signaling [43, 44, 45, 46 and 47]. When pretreated with a nAChR blocker, no increase in DA release was observed after nicotine administration [48, 49]. Moreover, knockout mice lacking the nAChR $\beta 2$ -subunit show no increased DA levels in dorsal and ventral striatum and fail to maintain nicotine selfadministration as compared to wild-type siblings [50, 51]. Additionally, the presence of $\alpha 4$ -containing-nAChRs is sufficient for nicotine-induced reward, tolerance and sensitization [52]. In summary, stimulation of the nAChRs results in increases in extracellular DA, an effect that seems to be dependent on the presence of $\alpha 4\beta 2$ nAChRs, and is blocked by nAChR blockers such as mecamylamine.

Role of nicotinic acetylcholine receptors in drug dependence

A direct and indirect role for nAChRs in drug dependence has been observed. For example, nAChRs are found in the hippocampus, where they directly facilitate the flow of excitatory information through the process of synaptic strengthening or Long-Term Potentiation (LTP) [53, 54 and 55]. LTP is a process contributing to the maintenance of drug dependence and relapse through cellular mechanisms important in learning and memory [55, 56]. In addition, nAChRs are present in the frontal cortex, where they are directly implicated in attention, memory, and associative learning [57, 58]. Indirectly, nAChR activation influences neurotransmitter systems, such as the choline, glutamate, norepinephrine, DA, serotonin, GABA, and endocannabinoid systems, and these changes in turn affect cognitive functioning with a role in drug dependence. For example, the endocannabinoid system is implicated in reward association; glutamate projections in the VTA are related with the development of incentive sensitization for drug use and play a crucial role in cue-reactivity and relapse; the neurotransmitter serotonin and the serotonin-1A receptor are important in cue-induced locomotor behavior; and the GABAergic system modulates the efficiency of the reinforcing effects of a drug [59, 60, 61 and 62]. Finally, part of the DA signal is modulated by cholinergic input, and DA release associated with reward in drug dependence processes could thus be influenced by modulating the nAChR [63]. As mentioned previously, an increase in extracellular DA in the NcA due to nAChR activation appears to be associated with the rewarding and addictive properties not only of nicotine, but also of other psychostimulant drugs of abuse, such as cocaine and amphetamine [64]. Furthermore, we cannot exclude that different neurotransmitter systems activated through the nAChRs, could themselves activate the DA system. This could be executed through intermediate inhibitory GABAergic and excitatory glutamatergic synapses and would lead to a further regulation of the activity of DA cells in the VTA and downstream on the reward system. Through nAChR activation, nicotine enhances the actions of glutamate and DA, thus providing a potential mechanism of action for the addictive properties of the drug. Different studies provide evidence that modulating nAChRs could play a more general role in drug dependence and is not limited to just nicotine dependence. Exposure of whole cells to ethanol for only 3h resulted in long-lasting changes in nAChR expression levels that remained elevated for nearly a week following withdrawal [65]. Also, polymorphisms in the $\beta 2$ subunit

gene of the nAChR were found to be associated with subjective responses to alcohol looked at the density and distribution of DA terminal arbors, using $\alpha 4$ subunit knockout mice [66]. Cocaine, amphetamine, haloperidol or nicotine was administered for 8 weeks in order to assess the role of the $\alpha 4$ nAChR in regulating the arbor size of DAergic neurons. The results showed normal functioning of DA D2 receptor signaling in $\alpha 4$ knockout mice, but reduced reuptake of DA and an altered profile of the DA transporter (DAT). This study provides additional evidence for a role of nAChRs in altering DA response, specifically by regulating terminal arbor size of DA neurons [67]. Additionally, in opiate dependence, nAChRs in the VTA seem to be important for modulating morphine-state-dependent learning [68]. In summary, nAChRs seem to contribute to the development of drug dependence both directly and indirectly. Nicotinic AChRs contribute to hippocampal LTP important for learning and memory, processes that are crucial for the development of drug dependence. Indirectly, nAChRs activate the terminal fields of the DA reward system in the brain that contribute to persistence of drug dependence.

CONCLUSION

Although significant advances have been made over the past several decades in the development of effective treatments for addictions, they remain substantial public health problems. The development of neuroscience methodologies is still to improve for understanding the neuronal mechanisms and treatment. Concurrent investigation of substance and non-substance addictions should be especially informative.

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REFERENCES

1. Terwilliger, R. Z., Beitner-Johnson, D., Sevarino, K. A., Crain, S. M., & Nestler, E. J. A general role for adaptations in G-proteins and the cyclic AMP system in mediating the chronic actions of morphine and cocaine on neuronal function. *Brain Res* 1991; 548(1-2): 100-110.
2. Carlezon, W. A., Duman, R. S., & Nestler, E. J. The many faces of CREB. *Trends Neurosci* 2005; 28(8): 436-445, doi:10.1016/j.tins.2005.06.005.
3. Dinieri, J. A., Nemeth, C. L., Parsegian, A., Carle, T., Gurevich, V. V., Gurevich, E., et al. Altered sensitivity to rewarding and aversive drugs in mice with inducible disruption of cAMP response element-binding protein function within the nucleus accumbens. *J Neurosci* 2009; 29 (6): 1855-1859, doi:10.1523/JNEUROSCI.5104-08.2009.
4. Ang, E., Chen, J., Zagouras, P., Magna, H., Holland, J., Schaeffer, E., et al. Induction of nuclear factor-kappaB in nucleus accumbens by chronic cocaine administration. *J Neurochem* 2001; 79 (1): 221-224.
5. Nestler, Eric J. Common molecular and cellular substrates of addiction and memory. *Neurobiol Learn Mem* 2002; 78(3): 637-647.
6. LeFoll, B., Diaz, J., & Sokoloff, P. A single cocaine exposure increases BDNF and D3 receptor expression: implications for drug conditioning. *Neuro report* 2005; 16(2): 175-178.
7. Tsai, S.-J. Increased central brain derived neurotrophic factor activity could be a risk factor for substance abuse: Implications for treatment. *Med Hypotheses* 2007; 68(2): 410-414, doi: 10.1016/j.mehy.2006.05.035.
8. Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Gatley, S.J., Wong, C., Hitzemann, R., Pappas, N.R. Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D (2) receptors. *J. Pharmacol. Exp. Ther.* 1999; 291: 409-415.
9. Schultz, W. Behavioral theories and the neurophysiology of reward. *Annu. Rev. Psychol.* 2006; 57: 87-115. Schultz, W. Behavioral dopamine signals. *Trends Neurosci.* 2007; 30: 203-210.
10. Volkow, N.D., Wang, G.J., Telang, F., Fowler, J.S., Logan, J., Jayne, M., Ma, Y., Pradhan, K., Wong, C. Profound decreases in dopamine release in striatum in detoxified alcoholics: possible orbitofrontal involvement. *J. Neurosci.* 2007; 27: 12700-12706.
11. Franken, I.H., Booij, J., van den Brink, W. The role of dopamine in human addiction: from reward to motivated attention. *Eur. J. Pharmacol.* 2005; 526: 199-206.
12. Berridge, K.C. Robinson, T.E., The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res.* 1993; 18: 247-291.
13. Franken, I.H., Hendriks, V.M., Stam, C.J., van den Brink, W. A role for dopamine in the processing of drug cues in heroin dependent patients. *Eur. Neuropsychopharmacol.* 2004; 14: 503-508.
14. Everitt, B. J., & Robbins, T. W. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci.* 2005; 8(11): 1481-1489, doi: 10.1038/nn1579.
15. Childress, A. R., Mozley, P. D., McElgin, W., Fitzgerald, J., Reivich, M., & O'Brien, C. P. Limbic activation during cue-induced cocaine craving. *Am. J. Psychiatry* 1999; 156(1): 11-18.
16. Berke, J.D., and Hyman, S.E. Addiction, dopamine, and the molecular mechanisms of memory. *Neuron* 2000; 2: 515-532.
17. Hyman, S.E., and Malenka, R.C. Addiction and the brain: the neurobiology of compulsion and its persistence. *Nat. Rev. Neurosci.* 2001; 2: 695-703.
18. Kelley, A.E., and Berridge, K.C. The neuroscience of natural rewards: relevance to addictive drugs. *J. Neurosci.* 2002; 22: 3306-3311.
19. Koob, G.F., and Le Moal, M. Drug abuse: hedonic homeostatic dysregulation. *Science* 1997; 278: 52-58.
20. Silva, A.J., Kogan, J.H., Frankland, P.W., and Kida, S. CREB and memory. *Annu. Rev. Neurosci.* 1998; 21: 127-148.
21. Greengard, P., Nairn, A.C., Girault, J.A., Ouimet, C.C., Snyder, G.L., Fisone, G., Allen, P.B., Fienberg, A., and Nishi, A. The DARPP 32/protein phosphatase-1 cascade: a model for signal integration. *Brain Res.* 1998; *Brain Res. Rev.* 26: 274-284.
22. Das, S., Grunert, M., Williams, L., and Vincent, S.R. NMDA and D1 receptors regulate the phosphorylation of CREB and the induction of c-fos in striatal neurons in primary culture. *Synapse* 1997; 25: 227-233.
23. Konradi, C., Leveque, J.C., and Hyman, S.E. Amphetamine and dopamine-induced immediate early gene expression in striatal plastic neurons depends on postsynaptic NMDA receptors and calcium. *J. Neurosci.* 1996; 16: 4231-4239.
24. Liste, I., Guerra, M.J., Caruncho, H.J., and Labandeira-Garcia, J.L. Treadmill running induces striatal Fos expression via NMDA glutamate and dopamine receptors. *Exp. Brain Res.* 1997; 115: 458-468.
25. Steiner, H., and Kitai, S.T. Regulation of rat cortex function by D1 dopamine receptors in the striatum. *J. Neurosci.* 2000; 20: 5449-5460.
26. Steward, O., and Worley, P.F. Selective targeting of newly synthesized Arc mRNA to active synapses requires NMDA receptor activation. *Neuron* 2001; 30: 227-240.
27. Wang, J.Q., Daunais, J.B., and McGinty, J.F. NMDA receptors mediate amphetamine-induced upregulation of zif/268 and prepro dynorphin mRNA expression in rat striatum. *Synapse* 1994; 18: 343-353.
28. Jones, B.E., Halaris, A.E., McIlhany, M., & Moore, R.Y. Ascending projections of the locus coeruleus in the rat. I. Axonal transport in central noradrenalin neurons. *Brain Res.* 1977; 127(1): 1-27.
29. Swanson, L. W., & Hartman, B. K. The central adrenergic system. An immuno-fluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-beta-hydroxylase as a marker. *J. Comp. Neural* 1975; 163 (4): 467-505, doi:10.1002/cne.901630406.
30. Bruinvels AT, Palacios JM, Hoyer D. Autoradiographic characterisation and localisation of 5-HT1D compared to 5-HT1B binding sites in rat brain. *Naunyn Schmiedebergs Arch Pharmacol.* 1993; 347: 569-582.
31. Hjorth S, Tao R. The putative 5-HT1B receptor agonist CP-93,129 suppresses rat hippocampal 5-HT release in vivo: comparison with RU 24969. *Eur. J. Pharmacol.* 1991; 209: 249-252.

32. Morikawa H, Manzoni OJ, Crabbe JC, Williams JT. Regulation of central synaptic transmission by 5-HT_{1B} auto- and heteroreceptors. *Mol Pharmacol.* 2000; 58: 1271–1278.
33. Itier, V., Bertrand, D. Neuronal nicotinic receptors: from protein structure to function. *FEBS Lett.* 2001; 504: 118–125.
34. Changeux, J.P., Bertrand, D., Corringier, P.J., Dehaene, S., Edelstein, S., Lena, C., Le, N.N., Marubio, L., Picciotto, M., Zoli, M. Brain nicotinic receptors: structure and regulation, role in learning and reinforcement. *Brain Res.* 1998; *Brain Res. Rev.* 26: 198–216.
35. Flores, C.M., Rogers, S.W., Pabreza, L.A., Wolfe, B.B., Kellar, K.J. A subtype of nicotinic cholinergic receptor in rat brain is composed of alpha 4 and beta 2 subunits and is up-regulated by chronic nicotine treatment. *Mol. Pharmacol.* 1992; 41: 31–37.
36. Gopalakrishnan, M., Monteggia, L.M., Anderson, D.J., Molinari, E.J., Piattoni-Kaplan, M., Donnelly-Roberts, D., Arneric, S.P., Sullivan, J.P. Stable expression, pharmacologic properties and regulation of the human neuronal nicotinic acetylcholine alpha 4 beta 2 receptor. *J. Pharmacol. Exp. Ther.* 1996; 276: 289–297.
37. Wonnacott, S., Sidhpura, N., Balfour, D.J. Nicotine: from molecular mechanisms to behaviour. *Curr. Opin. Pharmacol.* 2005; 5: 53–59.
38. McGehee, D.S., Role, L.W. Presynaptic ionotropic receptors. *Curr. Opin. Neurobiol.* 1996; 6: 342–349.
39. Balfour, D.J. The neurobiology of tobacco dependence: a preclinical perspective on the role of the dopamine projections to the nucleus accumbens [corrected]. *Nicotine Tob. Res.* 2004; 6: 899–912.
40. Schoffeleer, A.N., De Vries, T.J., Wardeh, G., van de Ven, H.W., Vanderschuren, L.J. Psychostimulant-induced behavioral sensitization depends on nicotinic receptor activation. *J. Neurosci.* 2002; 22: 3269–3276.
41. Clarke, P.B., Pert, A. Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. *Brain Res.* 1985; 348: 355–358.
42. Zhou, F.M., Wilson, C., Dani, J.A. Muscarinic and nicotinic cholinergic mechanisms in the mesostriatal dopamine systems. *Neuroscientist* 2003; 9: 23–36.
43. Dani, J.A., De Biasi, M. Cellular mechanisms of nicotine addiction. *Pharmacol. Biochem. Behav.* 2001; 70: 439–446.
44. Di Chiara, G. Role of dopamine in the behavioural actions of nicotine related to addiction. *Eur. J. Pharmacol.* 2000; 393: 295–314.
45. Pidoplichko, V.I., DeBiasi, M., Williams, J.T., Dani, J.A. Nicotine activates and desensitizes midbrain dopamine neurons. *Nature* 1997; 390: 401–404.
46. Rapier, C., Lunt, G.G., Wonnacott, S. Stereoselective nicotine-induced release of dopamine from striatal synaptosomes: concentration dependence and repetitive stimulation. *J. Neurochem.* 1988; 50: 1123–1130.
47. Rice, M.E., Cragg, S.J. Nicotine amplifies reward-related dopamine signals in striatum. *Nat. Neurosci.* 2004; 7: 583–584.
48. Giorguieff-Chesselet, M.F., Kemel, M.L., Wandscheer, D., Glowinski, J. Regulation of dopamine release by presynaptic nicotinic receptors in rat striatal slices: effect of nicotine in a low concentration. *Life Sci.* 1979; 25: 1257–1262.
49. Imperato, A., Mulas, A., Di Chiara, G. Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. *Eur. J. Pharmacol.* 1986; 132: 337–338.
50. Marubio, L.M., Gardier, A.M., Durier, S., David, D., Klink, R., Arroyo-Jimenez, M.M., McIntosh, J.M., Rossi, F., Champtiaux, N., Zoli, M., Changeux, J.P. Effects of nicotine in the dopaminergic system of mice lacking the alpha4 subunit of neuronal nicotinic acetylcholine receptors. *Eur. J. Neurosci.* 2003; 17: 1329–1337.
51. Picciotto, M.R., Zoli, M., Rimondini, R., Lena, C., Marubio, L.M., Pich, E.M., Fuxe, K., Changeux, J.P. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. *Nature* 1998; 391: 173–177.
52. Tapper, A.R., McKinney, S.L., Nashmi, R., Schwarz, J., Deshpande, P., Labarca, C., Whiteaker, P., Marks, M.J., Collins, A.C., Lester, H.A. Nicotine activation of alpha4* receptors: sufficient for reward, tolerance, and sensitization. *Science* 2004; 306: 1029–1032.
53. Cooke, S.F., Bliss, T.V. Plasticity in the human central nervous system. *Brain* 2006; 129: 1659–1673.
54. Gray, R., Rajan, A.S., Radcliffe, K.A., Yakehiro, M., Dani, J.A. Hippocampal synaptic transmission enhanced by low concentrations of nicotine. *Nature* 1996; 383: 713–716.
55. Jones, S., Sudweeks, S., Yakel, J.L. Nicotinic receptors in the brain: correlating physiology with function. *Trends Neurosci.* 1999; 22: 555–561.
56. Changeux, J.P., Bertrand, D., Corringier, P.J., Dehaene, S., Edelstein, S., Lena, C., Le, N.N., Marubio, L., Picciotto, M., Zoli, M. Brain nicotinic receptors: structure and regulation, role in learning and reinforcement. *Brain Res.* 1998; *Brain Res. Rev.* 26: 198–216.
57. Levin, E.D., Simon, B.B. Nicotinic acetylcholine involvement in cognitive function in animals. *Psychopharmacology (Berl.)* 1998; 138: 217–230.
58. Pepeu, G., Giovannini, M.G. Changes in acetylcholine extracellular levels during cognitive processes. *Learn. Mem.* 2004; 11: 21–27.
59. Arnold, J.C. The role of endocannabinoid transmission in cocaine addiction. *Pharmacol. Biochem. Behav.* 2005; 81: 396–406.
60. Kalivas, P.W. Glutamate systems in cocaine addiction. *Curr. Opin. Pharmacol.* 2004; 4: 23–29.
61. Muller, C.P., Carey, R.J., Salloum, J.B., Huston, J.P. Serotonin1A-receptor agonism attenuates the cocaine-induced increase in serotonin levels in the hippocampus and nucleus accumbens but potentiates hyperlocomotion: an in vivo microdialysis study. *Neuropharmacology* 2003; 44: 592–603.
62. Roberts, D.C. Preclinical evidence for GABAB agonists as a pharmacotherapy for cocaine addiction. *Physiol. Behav.* 2005; 86: 18–20.
63. Keith, J.R., Iacoviello, M.P., Barrett, L.E., Mansvelder, H.D., McGehee, D.S. Differential modulation by nicotine of substantia nigra versus ventral tegmental area dopamine neurons. *J. Neurophysiol.* 2007; 98: 3388–3396.
64. Kelley, A.E. Nicotinic receptors: addiction's smoking gun? *Nat. Med.* 2002; 8: 447–449.
65. Dohrman, D.P., Reiter, C.K. Ethanol modulates nicotine induced upregulation of nAChRs. *Brain Res.* 2003; 975: 90–98.
66. Ehringer, M.A., Clegg, H.V., Collins, A.C., Corley, R.P., Crowley, T., Hewitt, J.K., Hopfer, C.J., Krauter, K., Lessem, J., Rhee, S.H., Schlaepfer, I., Smolen, A., Stallings, M.C., Young, S.E., Zeiger, J.S. Association of the neuronal nicotinic receptor beta2 subunit gene (CHRNA2) with subjective responses to alcohol and nicotine. *Am. J. Med. Genet., B Neuropsychiatr. Genet.* 2007; 144B: 596–604.
67. Parish, C.L., Nunan, J., Finkelstein, D.I., McNamara, F.N., Wong, J.Y., Waddington, J.L., Brown, R.M., Lawrence, A.J., Horne, M.K., Drago, J. Mice lacking the alpha4 nicotinic receptor subunit fail to modulate dopaminergic neuronal arbors and possess impaired dopamine transporter function. *Mol. Pharmacol.* 2005; 68: 1376–1386.
68. Rezayof, A., Darbandi, N., Zarrindast, M.R. Nicotinic acetylcholine receptors of the ventral tegmental area are involved in mediating morphine-state-dependent learning. *Neurobiol. Learn. Mem.* 2008; 90: 255–260.