Behavioural Brain Research 277 (2015) 146–192

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

The role of serotonin in drug use and addiction

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HIGHLIGHTS

- We review the role of the serotonergic system in the establishment of psychoactive drug use and transition to addiction.
- There is a distinct involvement of the serotonergic system in both processes.
- A new functional model suggests specific serotonergic adaptations during controlled drug use.
- Induced serotonergic adaptations render the nervous system susceptible to the transition to compulsive drug use.
- Serotonergic adaptations often overlap with genetic risk factors for addiction.

ARTICLE INFO

Article history:
Received 13 March 2014
Received in revised form 4 April 2014
Accepted 5 April 2014
Available online 25 April 2014

Keywords:
Serotonin
Psychoactive drug
Abuse
Addiction
Animal model
Genetic risk

ABSTRACT

The use of psychoactive drugs is a wide spread behaviour in human societies. The systematic use of a drug requires the establishment of different drug use-associated behaviours which need to be learned and controlled. However, controlled drug use may develop into compulsive drug use and addiction, a major psychiatric disorder with severe consequences for the individual and society. Here we review the role of the serotonergic (5-HT) system in the establishment of drug use-associated behaviours on the one hand and the transition and maintenance of addiction on the other hand for the drugs: cocaine, amphetamine, methamphetamine, MDMA (ecstasy), morphine/heroin, cannabis, alcohol, and nicotine. Results show a crucial, but distinct involvement of the 5-HT system in both processes with considerable overlap between psychostimulant and opioidergic drugs and alcohol. A new functional model suggests specific adaptations in the 5-HT system, which coincide with the establishment of controlled drug use-associated behaviours. These serotonergic adaptations render the nervous system susceptible to the transition to compulsive drug use behaviours and often overlap with genetic risk factors for addiction. Altogether we suggest a new trajectory by which serotonergic neuroadaptations induced by first drug exposure pave the way for the establishment of addiction.

Contents

Abbreviations: AMPH, amphetamine; CPA, conditioned place aversion; CPP, conditioned place preference; CS, conditioned stimulus; CSF, cerebrospinal fluid; DA, dopamine; DCC, dopa decarboxylase; THC, tetrahydrocannabinol; DRN, dorsal raphe nucleus; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; 5-HTP, 5-hydroxy-*L*-tryptophane; *5-HTT*, serotonin transporter coding gene; 5-HTTLPR, insertion/deletion polymorphism in the serotonin transporter gene promoter region; FC, frontal cortex; GTP, guanosine triphosphate; ICSS, intracranial self-stimulation; IPSP, inhibitory postsynaptic potential; LgA, long access rats; MAPK, mitogen-activated protein kinase; MDMA, 3,4-methylenedioxymethamphetamine; METH, methamphetamine; MAO-A, monoamine oxidase A; MRN, median raphe nucleus; NA, noradrenaline; Nac, nucleus accumbens; PET, positron emission tomography; PFC, prefrontal cortex; SSRI, selective serotonin reuptake inhibitor; SERT, serotonin transporter; ShA, short access rats; SN, substantia nigra; SNP, single nucleotide polymorphism; 3′-UTR, 3′-untranslated region; TPH, tryptophan hydroxylase; VNTR, variable number tandem repeat; VTA, ventral tegmental area.

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http://dx.doi.org/10.1016/j.bbr.2014.04.007
0166-4328/