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Review article

Obsessive-compulsive disorder: Insights from animal models☆

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ABSTRACT

Research with animal models of obsessive-compulsive disorder (OCD) shows the following: (1) Optogenetic studies in mice provide evidence for a plausible cause-effect relation between increased activity in cortico-basal ganglia-thalamo-cortical (CBGTC) circuits and OCD by demonstrating the induction of compulsive behavior with the experimental manipulation of the CBGTC circuit. (2) Parallel use of several animal models is a fruitful paradigm to examine the mechanisms of treatment effects of deep brain stimulation in distinct OCD endophenotypes. (3) Features of spontaneous behavior in deer mice constitute a rich platform to investigate the neurobiology of OCD, social ramifications of a compulsive phenotype, and test novel drugs. (4) Studies in animal models for psychiatric disorders comorbid with OCD suggest comorbidity may involve shared neural circuits controlling expression of compulsive behavior. (5) Analysis of compulsive behavior into its constitutive components provides evidence from an animal model for a motivational perspective on OCD. (6) Methods of behavioral analysis in an animal model translate to dissection of compulsive rituals in OCD patients, leading to diagnostic tests.

Contents

Abbreviations: 5-HT, serotonin; ACC, anterior cingulate cortex; AAV, adenovirus-associated vector; DBS, deep brain stimulation; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; cAMP, cyclic adenosine-monophosphate; CBGTC, cortico-basal ganglia-thalamo-cortical; ChR2, channelrhodopsin; DA, dopamine; DPAT, 8-hydroxy-2-(di-*n*-propylamino) tetralin hydrochloride; EP, entopeduncular nucleus; EWMN, Eshkol-Wachman Movement Notation; EYFP, enhanced yellow fluorescent protein; fMRI, functional magnetic resonance imaging; FT, fixed time; GABA, γ-amino butyric acid; GSH, glutathione; GP, globus pallidus; GPi, internal segment of the globus pallidus; H, high stereotypic (deer mice); LGP, lateral globus pallidus; mPFC, medial prefrontal cortex; N, non-stereotypic (deer mice); NAc, nucleus accumbens; NB, nest-building; NMDA, N-methyl-D-aspartate; OC, obsessive-compulsive; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PDE, phosphodiesterase; PFC, prefrontal cortex; QNP, quinpirole; SA, signal attenuation; Schizo-OCD, comorbid schizophrenia and obsessive-compulsive disorder; SERT, serotonin transporter; SIP, schedule-induced polydipsia; SSRI, serotonin-selective reuptake inhibitor; STN, subthalamic nucleus; VI, variable interval; VMS, ventromedial striatum.

☆ Based on a symposium with the same title (co-chairs: HS, RJB) at the International Behavioral Neuroscience Society (IBNS) meeting held in Victoria, BC, Canada. Each major section describes the work in the laboratories of the investigators; the sequence of sections in the paper is conceptual. All authors contributed equally to the writing of this paper.

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1. Introduction

Animal models of psychiatric disorders simulate signs or symptoms of a psychiatric disorder to provide a preparation for testing specific etiological theories and underlying mechanisms of the disorder as well as for conducting preclinical drug evaluations (Eilam and Szechtman, 2005a; Jones et al., 2011; Lazar et al., 2011; McKinney, 1988; Szechtman and Eilam, 2005; Willner, 1984). The use of animal models in psychiatry has had a stormy history in part because of the need to work out their proper place in the context of psychiatry as a scientific discipline (Szechtman and Eilam, 2005). One challenge often levelled at animal models is scepticism that the model fully replicates the clinical condition or bears relevance for the mechanisms of the human condition. Attempts at dealing with this challenge led to influential formulations of criteria to evaluate animal models in psychiatry (Abramson and Seligman, 1977; Belzung and Lemoine, 2011; Geyer and Markou, 1995; Hoffman, 2016b; McKinney and Bunney, 1969; Willner, 1984, 2005; Willner et al., 1992). While the use of animal models in psychiatry is accepted as proper today, it is worthwhile to reiterate briefly what constitutes a “model.”

A scholarly exposition regarding what a “model” is and the “tortuous” history of models in psychology was provided by Chapanis (1961). Of relevance to the present review using animal models of OCD, Chapanis (1961) pointed out that a model is “. . .only an analogy, a statement that in some ways the thing modeled behaves ‘like this’ (p. 188). Indeed, “. . .the worst error committed in the name of models is to forget that at best a model represents only a part – and usually only a small part – of the thing being modeled” (Chapanis, 1961 p. 126). The same notion had been echoed by McKinney (1988), in *Models of Mental Disorders: A New Comparative Psychiatry*, who admonished against the quest for comprehensive animal models of psychiatric disorders because no model can be a miniature replica of the entire human condition. Unfortunately, even today this crucial point is not always remembered. Chapanis (1961) has argued that because of their inherently limited scope, models should be evaluated differently from theories: “Models, in a word, are judged by criteria of usefulness; theories, by criteria of truthfulness” (p. 119). In other words, good models generate novel insights and new research. Of course, models designed to test particular theory regarding an aspect of the human disorder are evaluated by criteria of both usefulness and truthfulness.