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Using animal models to develop therapeutics for Tourette Syndrome

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Abstract

The science of Tourette Syndrome (TS) is advancing at multiple levels of analysis and will be enhanced through the use of animal models. Particular challenges in the development of TS animal models reflect complex features of this disorder, including its waxing and waning course and its "invisible" sensory and psychic symptoms. Animal models can achieve face, predictive, or construct validity based on their particular features. Predictive validity, of most direct relevance to drug development for TS, is achieved to some degree by a several animal models, although the reliance of most of these models on measures of motor suppression may ultimately limit their utility. Other models achieve construct validity with proposed pathophysiological mechanisms related to the immune and neural circuit etiologies of TS. One model – deficient sensorimotor gating of the startle reflex – is discussed in terms of its present and future applications towards advancing our understanding of the pathophysiology and treatment of TS. In addition to models that will advance the pharmacotherapy of TS, other animal models may enhance the utility of nonpharmacologic TS treatments, ranging from behavior therapy to deep brain stimulation (DBS).

Keywords: Animal model; Basal ganglia; Dopamine; Prepulse inhibition; Sensorimotor gating; Tourette Syndrome

Abbreviations: APO, apomorphine; CSPT, cortico-striato-pallido-thalamic; DA, dopamine; DBS, deep brain stimulation; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; EPS, extrapyramidal side effects; ERP, exposure and response prevention; GABHS, group A beta-hemolytic streptococcus; GPe, external globus pallidus; HRT, habit reversal therapy; NE, norepinephrine; NMDA, *n*-methyl-D-aspartate; OCD, obsessive compulsive disorder; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcus; PPI, prepulse inhibition; TS, Tourette Syndrome; TSA, Tourette Syndrome Association; YGTSS, Yale Global Tic Severity Scale.

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1. Introduction

Advances in our understanding of Tourette Syndrome (TS) are occurring at multiple levels of analysis. Genetic studies have determined that TS is polygenic, and candidate regions of the genome are being targeted for fine mapping. Neuroimaging studies have identified both striatal volumetric and neurochemical abnormalities in TS populations, and efforts are underway to enhance the resolution of these signals via refined experimental designs and technologies, to understand their functional implications, and link them to genes. Clinical trials have identified novel pharmacological and behavioral approaches to treating TS. Even neuropathological studies, hindered by many features of this childhood developmental disorder, are beginning to find cellular pathology that is consistent with regional abnormalities detected via neurochemical imaging. Other areas of TS science, including the putative link between TS and autoimmune processes, remain the focus of active investigation.

Progress at each of these levels of analysis would accelerate with the development and implementation of preclinical models of TS. Three common types of preclinical models involve either normal human subjects, "infrahuman" (animal) subjects, or "in silico" (computer/artificial intelligence) subjects. Of these, animal models are the ones most widely applied to studying neuropsychiatric disorders, particularly with the aim of developing therapeutics.

One major hurdle in clinical studies of TS results from the fact that TS is relatively rare and more heterogeneous than was once appreciated. TS studies are slowed by difficulties in subject recruitment and are often "underpowered" with small cohorts that differ in age, sex, comorbid diagnoses, medication history, and many other undocumented variables (e.g., history of perinatal complications or recurrent streptococcal infections). In contrast, an experimenter can, in a matter of days or weeks, study large numbers of animals that are identical in their genetics, age, sex, home environment, exposure (or lack thereof) to medications or infections, and so on.

The utility of animal models, in part, reflects the fact that we are more like "lower species" than we may want to admit. Certainly, most genes and brain substrates of relevance to TS are shared among humans, infrahuman primates, and rodents. More than 90% of the mouse genome is shared by humans, and while brain structures differ, particularly within later developing cortical regions, much of the basic "wiring diagram" of cortico-striato-pallido-thalamic (CSPT) circuitry is conserved across these species. Therefore, many hypotheses regarding biological mechanisms in TS–from gene to protein to cell to system–can be tested using infrahuman models.

Most medications for human disorders are developed without a complete understanding of pathogenesis; certainly, this is true for TS. Drug development strategies need not be strictly bound to a comprehensive hypothesis or disease model. Still, as discussed below, these strategies can benefit greatly from advances in our understanding of TS pathophysiology, or even from a greater understanding of the normal physiology of neural systems thought to be involved in the genesis of TS.

Specific issues in animal model development have particular relevance for TS therapeutics. For example, most predictive models focus on acute drug effects. With some notable exceptions, clinical benefit from medications in TS evolves over time, as is the case with medication responses in a number of different neuropsychiatric disorders. This "disconnect" between the acute effectiveness of drugs in the animal model versus the need for sustained treatment in the clinical condition also suggests a disconnection between drug mechanism in the model versus in the disorder. This issue characterizes many preclinical models (e.g., the same is true for most models that predict antipsychotic medications; Freedman & Giarman, 1956; Swerdlow et al., 1994). Based on this disconnect, it seems likely that viable TS candidate drugs–ones acting through mechanisms more directly linked to their clinical efficacy–might be rejected by acute predictive models, but might otherwise be detected using models that employ chronic dosing schedules.

The development of predictive drug models for TS is also complicated by the difficulty verifying "true positive" responses in clinical trials. Part of this difficulty reflects the normal waxing and waning pattern of TS symptoms (Peterson & Leckman, 1998). Patients typically present for treatment during a period of symptom exacerbation, which, based on a sinusoidal-like pattern of symptom severity in TS, would naturally be followed by a period of relative remission. As this natural course progresses, symptom reduction is often inappropriately attributed to treatments that were initiated during the exacerbation phase. The process continues, with dose adjustments and, ultimately, medication changes accompanying successive periods of symptom exacerbation. While efforts have been made to model the periodicity of tic symptoms in silico and in vivo (Peterson & Leckman, 1998), the complexity of these models (e.g., oscillatory neuronal discharge patterns) presents a challenge for rapid throughput drug screening. Clinically, these temporal patterns lead to an abundance of unreliable anecdotal reports of positive treatment responses and to many superstitions–about medications and about the physicians who prescribe them–that are based on erroneous causal associations. Perhaps, more so than with other common neuropsychiatric disorders, there are an impressive number of idiosyncratic/individualized therapeutic responses and nonresponses in TS, making it very difficult to unequivocally reject or endorse the therapeutic potential of any given drug for any given patient, even armed with data from relatively large, controlled clinical trials.