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Genetic animal models of dystonia: Common features and diversities

Franziska Richter, Angelika Richter *

Institute of Pharmacology, Pharmacy and Toxicology, Department of Veterinary Medicine, University of Leipzig, 04103 Leipzig, Germany

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ABSTRACT

Animal models are pivotal for studies of pathogenesis and treatment of disorders of the central nervous system which in its complexity cannot yet be modeled in vitro or using computer simulations. The choice of a specific model to test novel therapeutic strategies for a human disease should be based on validity of the model for the approach: does the model reflect symptoms, pathogenesis and treatment response present in human patients? In the movement disorder dystonia, prior to the availability of genetically engineered mice, spontaneous mutants were chosen based on expression of dystonic features, including abnormal muscle contraction, movements and postures. Recent discovery of a number of genes and gene products involved in dystonia initiated research on pathogenesis of the disorder, and the creation of novel models based on gene mutations. Here we present a review of current models of dystonia, with a focus on genetic rodent models, which will likely be first choice in the future either for pathophysiological or for preclinical drug testing or both. In order to help selection of a model depending on expression of a specific feature of dystonia, this review is organized by symptoms and current knowledge of pathogenesis of dystonia. We conclude that albeit there is increasing need for research on pathogenesis of the disease and development of improved models, current models do replicate features of dystonia and are useful tools to develop urgently demanded treatment for this debilitating disorder.

Contents

Abbreviations: KI, knock-in; KO, knockout; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; DOPA, dihydroxyphenylalanine; DRD, dopa-responsive dystonia; GABA, γ-aminobutyric acid; 5-HT, serotonin; HVA, homovanillic acid; TH, tyrosine hydroxylase; D2R, dopamine receptor type 2; D1R, dopamine receptor type 1; DAT, dopamine transporter; PD, Parkinson's disease; PNKD, paroxysmal non-kinesiogenic dystonia.

* Corresponding author at: Institute of Pharmacology, Pharmacy and Toxicology, Department of Veterinary Medicine, University of Leipzig, An den Tierkliniken 15, 04103 Leipzig, Germany. Tel.: +49 3419738131; fax: +49 03419738149.
E-mail address: angelika.richter@vetmed.uni-leipzig.de (A. Richter).

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1. Introduction

More than 3 million people worldwide suffer from dystonia (Jinnah and Hess, 2008), the third most common movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation (Albanese et al., 2013). It can present isolated or in combination/co-occurrence with a large number of other neurological disorders, ranging from ataxia to Parkinson's disease (PD). Classification of the different representations of dystonia is challenging and has been modified extensively over the last 40 year (Albanese et al., 2013; Fahn, 2011). Current classification separates dystonia disorders by clinical characteristics (Axis I, age at onset, body distribution, temporal pattern and associated features) and etiology (Axis II, nervous system pathology, inherited or acquired).

It was estimated that for one third of cases a causative factor has been identified, whereby hereditary Dyt1 dystonia accounts for up to 90% of the early onset dystonia cases (Spatola and Wider, 2012). More than 20 different gene mutations, currently designated as DYT1-25 (Lohmann and Klein, 2013; Moghimi et al., 2013), related to dystonia are now isolated and have been extensively reviewed recently (Fuchs and Ozelius, 2011; Lohmann and Klein, 2013; Ozelius et al., 2011; Spatola and Wider, 2012). For more than half of these genes encoded proteins were identified (Fig. 1) and found to be involved in a broad range of functions, including dopamine signaling, protein chaperoning, transcriptional regulation or transporter proteins (Ledoux et al., 2013; Lohmann and Klein, 2013; Ozelius et al., 2011; Spatola and Wider, 2012). Penetrance of the most common subtype of inherited dystonia, DYT1, is not complete (Ghilardi et al., 2003), indicating the importance of environmental or additional genetic factors in pathophysiology. Such factors may increase probability of developing the symptoms or represent compensatory mechanisms in asymptomatic carriers, similar to what is described in some genetic forms of PD and PD animal models (Chesselet and Richter, 2011).

Similar interactions of gene mutations, genetic background and environmental factors may contribute to forms of late onset dystonia, which are generally more common. Recent genome wide association studies aimed to identify large effect-size risk loci in cervical dystonia suggested the involvement of a sodium leak channel (Mok et al., 2013). Prevalence of dystonia will further increase in association with age related diseases like PD, due to the prolongation of life span. Currently PD already affects more than 2% of the population above 65 years of age. In PD, a retrospective observational study showed that a third of patients had a deformity of their limbs, neck, or trunk, which are refractory to L-DOPA treatment and can present early in PD disease progression (Doherty et al., 2011). Furthermore, dystonia can present together or in sequence with PD (Spatola and Wider, 2012). In fact, in the population over 50 years of age dystonia can be defined as a common neurological disorder, placing it among the top disorders to impact quality of life and health care costs in aging societies (Phukan et al., 2011). Furthermore, dystonia can be acquired through medications, toxins, trauma, brain tumors or viral infection (Breakefield et al., 2008).

Unfortunately, pharmacological treatment of the different clinical types of dystonia is insufficient or ineffective in most cases and largely based on empirical, rather than scientific rationale (Jankovic, 2009). However, with the recent identification of the gene products of a number of mutations which cause dystonia (Fuchs and Ozelius, 2011; Lohmann and Klein, 2013), and the development of multiple rodent models, pathophysiological studies and pre-clinical drug screens become more feasible (Jinnah and Hess, 2008; Klein et al., 2011). A growing number of animal models of dystonia created on the basis of recently identified gene mutations that cause dystonia in humans, together with established rodent models that express dystonic postures or movements can be immensely helpful to uncover risk factors and pathophysiology of dystonia. The urgent need for improved and novel treatments demands further characterization of these models. However, similar to other disorders extensively modeled in animals, it cannot be expected that one animal model will encompass all features of such a complex and diverse disorder. Instead the current models should be viewed as tools to study and treat specific facets of the disorder.

Here, we will present an overview of current models organized by the features of dystonia they are required to express. In the first chapters we focus on motor dysfunction, dystonic postures and non-motor dysfunction by first describing the symptoms in human patients followed by the respective representation in animal models. Next we present current knowledge on neuropathology and pathophysiology in human dystonia, again discussing how this is reflected in respective animal models. This organization will aid readers to identify models which represent a specific aspect of the disease and could for example be used to develop therapeutic intervention. In our detailed description of the models for each chapter, we will focus on rodent models as first-line tools for the identification of drug targets and preclinical drug testing. In the final sections we will summarize and discuss the current invertebrate genetic models and pharmacological models in rodents and primates. Most relevant genetic models are described in detail in the text and in Table 1. Additional genetic and toxin or drug induced rodent models are briefly mentioned in the text and details are summarized in Table 1.

2. Motor dysfunction and dystonic postures

Dystonia is by definition a collection of symptoms which express mainly as hyperkinetic motor dysfunction including dystonic postures and movements, which at the peak of expression often overflow beyond primarily involved body region. Dystonic symptoms can occur constantly or paroxysmal, can get progressively worse, remain unchanged or alleviate with age. Postures may include extremities, the head or the body axis, whereas dystonic movements can develop out of a specific daily use or overuse of an extremity (Albanese et al., 2013; Fung et al., 2013). Specific *gestes antagonistes* may alleviate dystonia by simple touch of a body part or through smooth and natural movements (Phukan et al., 2011). Observations of underlying pathology or alterations in neurotransmission are challenging in humans (Quartarone and Hallett, 2013). Accordingly clinical studies of prospective novel therapeutics will highly rely on improvement of these motor symptoms, which directly translates to preclinical trials as well. An animal model used for such preclinical trials has to offer a behavioral readout of underlying pathophysiology, which preferably relates to the symptomatology observed in the human patient.

2.1. Spontaneous mutants with expression of dystonic postures for preclinical drug testing

During the last decades several spontaneous mutations have been proposed as animal models of dystonia based on the phenotype (Table 1). Limitations consist in part in a reduced vitality and the occurrence of other neurological signs, such as epilepsy, severe ataxia or muscle weakness. A strong readout with good effect size and sufficient power to test drug effects is known in the dt^{sz} mutant hamster, which shows the clinical characteristics of primary paroxysmal dystonia, including co-contractions of