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NEWS & VIEWS

Orofacial dyskinesias and dystonia in rats infected with Borna disease virus; a model for tardive dyskinetic syndromes

The neurochemical and lesion effects of Borna disease virus infection in rats result in a syndrome with phenotypic and pharmacological similarities to tardive dyskinesia.

Tardive dyskinesia (TD) is a hyperkinetic movement disorder that occurs in 20–30% of patients who receive chronic treatment with conventional neuroleptics.[1] TD classically manifests as orofacial dyskinesias (repetitive chewing movements, lip smacking, tongue protrusions or lip puckering).[2] However, repetitive movements of other parts of the body trunk or respiratory muscle groups, tics, tardive dystonia,[3] tardive stereotypy[4] and tardive akathisia[5] (a feeling of inner restlessness) are also described.

Risk factors including age, female gender, organic brain dysfunction, early extrapyramidal side-effects, mood disorders and substance abuse have been identified.[1] However, the underlying pathophysiology, factors affecting the timecourse of disease, and the reasons for heterogeneity of disease expression, remain incompletely understood. Proposed mechanisms for TD include: striatal dopamine (DA) receptor hyperplasia and supersensitivity;[2,6,7] post-synaptic signal enhancement;[8] increased striatal glutamate release;[9] decreased GABAergic[10,11] or cholinergic activity;[12,13] peptidergic (opioid)[14] or lipid (cannabinoid)[15] neuromodulatory effects; and metabolic, heavy metal or oxyradical toxicity.[16–18]

Attempts to establish a small animal model of tardive dyskinesia have focused on pharmacologic manipulations of the dopamine system and lesion studies. Short-term (2–4 week) treatment of rats with DA receptor blockers produces rapid DA receptor proliferation[19] and orofacial dyskinesias after drug withdrawal.[20] Although this paradigm provides a model of pharmacologic 'disuse' or 'denervation' supersensitivity[20] and evidence of behavioral phenomena presumably related to DA synaptic supersensitivity, orofacial dyskinesias are seen only when animals are challenged with DA agonists. Thus, this experimental model differs from the human disorder, where expression is spontaneous.[11] Indeed, the protracted and often permanent course of TD does not support a mechanism based purely on a pharmacologic state of denervation supersensitivity. Long-term treatment (6–12 months) of rats with neuroleptics, including haloperidol, thioridazine, trifluoperazine, fluphenazine, *cis*-flupenthixol, or sulpiride, results in orofacial dyskinesias resembling TD.[8,21,22] However, because the vacuous chewing movements are aggravated by cholinergic agents and improved by anticholinergic drugs, these models may more accurately represent neuroleptic-induced acute dystonia than TD.[22] Similarly, the spontaneous jaw movements observed in rats following bifrontal cortical ablation and haloperidol administration also results in spontaneous jaw movements.[23,24] The syndrome responds acutely to haloperidol but is aggravated by cholinergic agonists,[24] again manifesting a pharmacologic profile more consistent with neuroleptic-induced acute dystonia than TD.

An alternative model of TD has been established in rats infected with the neurotropic virus, Borna disease virus (BDV). Infected rats have a chronic progressive encephalopathy that results in a syndrome with neurochemical similarities to schizophrenia and DA system effects functionally equivalent to D2 receptor blockade. This model affords new opportunities to examine hypotheses of CNS adaptations to DA manipulations to identify molecular, cellular, and neural system processes that contribute to dyskinetic syndromes.

Borna disease virus (BDV), the prototype of a newly recognized virus family (*Bornaviridae*) within the nonsegmented negative-strand RNA viruses, has a wide natural and experimental host range, including mammals and birds. Natural infection results in acute encephalitic illnesses of horses and sheep; experimental infection produces acute, subacute or chronic encephalitic illnesses (Borna disease, BD) in rodents, primates, and domestic mammals.[25] Although there are several reports suggesting an increase in prevalence of BDV infection in subjects with affective disorders or schizophrenia, the human epidemiology of BDV infection remains controversial.[25–27]

Immature adult rats infected with BDV develop a movement and behavior disorder characterized by oro-

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Table 1 Parallels between experimental Borna disease in rats and human TD

	BD-rat	*TD*
Signs	Orofacial dyskinesias Segmental or generalized dystonia Stereotypies	Orofacial dyskinesias Segmental or generalized dystonia Stereotypies
Clinical pharmacology	DA agonist enhancement Poor haldol response Good clozapine response Anticholinergic enhancement	DA agonist enhancement Poor conventional neuroleptic response at constant dose Good clozapine response Anticholinergic enhancement
Markers	DA denervation Compensatory DA presynaptic overactivity DA receptor pharmacologic supersensitivity Reduced D2 throughput Coexisting neuropathology	Pharmacologic DA denervation Compensatory DA presynaptic overactivity DA receptor pharmacologic supersensitivity Reduced D2 throughput Predisposing neuropathology

facial dyskinesias: vacuous chewing, repetitive mouth opening or puckering, lip smacking, licking, biting, scratching, forepaw jerks, retrocollis, torticollis or generalized dystonia. In some rats, the facial dyskinesias are dominant, whereas in others, axial or limb extrapyramidal signs are more prominent. The syndrome appears 6–8 weeks after infection and remains stable over a period of 3–4 months.[28] The dyskinetic movements tend to be repetitive in appearance and distribution, and may be suppressed during feeding and drinking. Thus, both BD and TD are distinct from the human choreic syndromes, which fail to suppress with concentration or during other motor activities.[29]

Responses to pharmacologic agents are also similar in BD and TD. The dyskinesias and stereotypies are aggravated by both direct and indirect DA agonists (apomorphine, D-amphetamine, cocaine), poorly responsive to D2 antagonists raclopride and haloperidol, but improved by the atypical neuroleptic clozapine.[28] Furthermore, as in TD,[30] and in contrast to other rat models of orofacial dyskinesias, BD is exacerbated by anticholinergics. Whereas the anticholinergic scopolamine (hydrobromide) increases vacuous chewing movements, licking of cage walls, and biting of wire cage floor of BD rats, the direct cholinergic agonist pilocarpine (hydrochloride) or the anticholinesterase physostigmine (salicylate) results in sedation of BD rats and amelioration of orofacial movements. Although the pharmacologic effects of GABAergic drugs in BD-rats have not yet been studied, decreased whole brain glutamic acid decarboxylase (GAD) messenger RNA described in brains of BD-rats,[31] predicts there may be a response to agents that enhance GABA transmission and secondarily inhibit DA systems.

Neurochemical and neuroanatomic analysis of BD rats suggests parallels to schizophrenia, and striatal receptor changes potentially link the BD model to TD. Consistent with some current neurotransmitter and circuit hypotheses of schizophrenia,[32–34] are the findings of mesolimbic DA hyperactivity (elevated DOPAC/DA ratios in nucleus accumbens and olfactory tubercle),[28] serotonergic hyperactivity (elevated 5-HIAA/5-HT ratios in striatum),[35] and disordered prefrontal function (high DOPAC/DA[36] and MHPG/NE ratios in prefrontal cortex) (Solbrig, Koob and Lipkin, unpublished) in BD rats. Indeed, the virus is widely distributed through limbic and monoaminergic circuits[28] and pathology is present at every level of limbic and corticostriato-pallido-thalamic circuit loops reported to be abnormal in schizophrenia.[37] Further analysis, inclusive of the nigrostriatal system, reveals postsynaptic effects of virus: reduced numbers of D2 receptors in caudate-putamen and nucleus accumbens, yet normal numbers of D1 receptors in the same structures.[28,38] The result is a DA system imbalance that is functionally equivalent to chronic D2 receptor blockade. Periventricular (striatal) volume loss, considered to be a risk factor for TD,[39] is also observed in BD rats.[28] Partial DA cell loss from the substantia nigra pars compacta, a neuropathologic finding analogous to subclinical Parkinsonism and another risk factor for TD, is demonstrated by loss of tyrosine hydroxylase-immunoreactive cells and confirmed by reduced DA in caudate-putamen and reduced mazindol binding to high affinity DA-reuptake sites in the caudate-putamen of BD-rats.[28,40] Parallels between experimental Borna disease and TD are summarized in Table 1.

In concert, these features support the utility of the BD-rat as a model of TD, particularly where TD occurs in the context of parenchymal volume loss due to neurodegeneration or neurodevelopmental damage and patients have a more complex repertoire of behavioral disturbances than those described in some other models of TD. The syndrome is accessible to pharmacological manipulation and can be measured using established paradigms. Indeed, responses to drugs like clozapine indicate that BD rats can serve as bioassays for neuroleptic sensitivity and efficacy, advancing the development of drugs with dissociate antipsychotic activity and extrapyramidal side-effects. The possibility that BDV and other neurotropic viruses may be implicated in the pathogenesis of a subset of patients

with neuropsychiatric diseases further underscores the significance of the model.

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