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Mechanism of Action of INGREZZA® (valbenazine) Capsules and INGREZZA® SPRINKLE (valbenazine) Capsules

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the mechanism of action (MOA) of INGREZZA and INGREZZA SPRINKLE.

INGREZZA and INGREZZA SPRINKLE are indicated in adults for the treatment of tardive dyskinesia (TD) and for the treatment of chorea associated with Huntington's disease (HD).[1]

The MOA of valbenazine in the treatment of TD and chorea associated with HD is unclear, though its pharmacology has been well characterized. Valbenazine is a selective vesicular monoamine transporter 2 (VMAT2) inhibitor.[2,3] VMAT2 is an integral presynaptic protein that regulates the packaging and subsequent release of dopamine and other monoamines from neuronal vesicles into the synaptic cleft.[3,4] It is believed that by inhibiting VMAT2 from packaging dopamine into synaptic vesicles for subsequent release, valbenazine and its active metabolite ([+]-α-dihydrotetrabenazine) reduce dopamine signaling on postsynaptic dopamine D2 receptors. Valbenazine and [+]-α-dihydrotetrabenazine are highly selective for VMAT2 with negligible affinity for post-synaptic receptors, such as the D2 receptor.[2-4]

Please click HERE for the animation of the proposed MOA of valbenazine.

Tardive Dyskinesia

The etiology and pathophysiology of TD have not been fully elucidated. One leading hypothesis implicates the post-synaptic dopamine D2 receptor upregulation that may result from exposure to dopamine receptor blocking agents (DRBAs), such as first- and second-generation antipsychotics and the gastric motility agent metoclopramide. This upregulation of D2 receptors is thought to result in post-synaptic dopamine hypersensitivity with the subsequent, aberrant neurotransmission manifesting as the abnormal, involuntary movements of TD.[5]

Chorea Associated with Huntington's Disease

Huntington's disease is a hereditary neurodegenerative disorder caused by an expansion of CAG repeats in the huntingtin gene, leading to an abnormal huntingtin protein. The exact mechanism of cell loss is unclear, but atrophy of the striatum due to the dysfunctional huntingtin protein may result in dysregulation of neurotransmission pathways, leading to an overstimulation of dopamine receptors and the precipitation of choreiform movements.[6,7]

This letter and the enclosed material are provided in response to your unsolicited medical information inquiry. Please feel free to contact Neurocrine Medical Information at (877) 641-3461 or medinfo@neurocrine.com if you would like to request additional information.

References:

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
2. Grigoriadis D, et al. Pharmacologic characterization of valbenazine (NBI-98854) and its metabolites. *J of Pharmacology and Experimental Therapeutics*. 2017; 361:454-461.
3. Grigoriadis D, et al. Pharmacologic Characteristics of valbenazine(NBI-98854) and its Metabolites. Poster presented at the annual meeting of the United States Psychiatric and Mental Health Congress; October 21-24, 2016; San Antonio, Texas.
4. Patel J, et al. Presynaptic control of striatal dopamine neurotransmission in adult vesicular monoamine transporter 2 (VMAT2) mutant mice. *J Neurochem.* 2003;85(4):898-910.

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5. Sayers AC, et al. Neuroleptic-induced hypersensitivity of striatal dopamine receptors in the rat as a model of tardive dyskinesias: effects of clozapine, haloperidol, loxapine and chlorpromazine. *Psychopharmacologia*.1975;41(2):97-104.
6. Cepeda C, Murphy KPS, Levine MS, et al. The Role of Dopamine in Huntington's Disease. *Prog Brain Res.* 2014;211:235-54.
7. Armstrong MJ, Miyasaki JM. Evidence-based guideline: Pharmacologic treatment of chorea in Huntington disease. 2012. Neurology 79(6):597-603

Enclosure:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
B. INGREZZA [Important Safety Information]. San Diego, CA: Neurocrine Biosciences, Inc.
C. Grigoriadis D, et al. Pharmacologic Characteristics of valbenazine (NBI-98854) and its Metabolites. Poster presented at the annual meeting of the United States Psychiatric and Mental Health Congress; October 21-24, 2016; San Antonio, Texas.