

## The mechanism of degeneration of striatal neuronal subtypes in Huntington disease

Azadeh A. Rikani<sup>1,3</sup>, Zia Choudhry<sup>1,2,4</sup>, Adnan M Choudhry<sup>4</sup>, Nasir Rizvi<sup>5</sup>, Huma Ikram<sup>6</sup>, Nusrat J Mobassarrah<sup>7</sup>, Sagun Tuli<sup>8</sup>

<sup>1</sup>Douglas Hospital Research Centre, Montreal, Quebec, Canada; <sup>2</sup>Department of Human Genetics, McGill University, Montreal, Quebec, Canada; <sup>3</sup>Department of Psychiatry, McGill University, Montreal, Quebec, Canada; <sup>4</sup>Division of Research and Medical Education, International Maternal and Child Health Foundation, Montreal, QC, Canada; <sup>5</sup>Department of Neurology, University of Alberta Hospital, University of Alberta, Edmonton, AB, Canada; <sup>6</sup>Neuropharmacology Research Unit, Department of Biochemistry, University of Karachi, Karachi, Pakistan; <sup>7</sup>Institute of Integrated Cell-Material Science, Kyoto University, Yoshida Ushinomiya-cho, Sakyo-ku, Japan; <sup>8</sup>Center for Advanced Brain & Spine Surgery, Boston, MA, USA, 01760.

### ABSTRACT

The pattern of neurodegeneration in Huntington's disease (HD) is very characteristic of regional locations as well as that of neuronal types in striatum. The different striatal neuronal populations demonstrate different degree of degeneration in response to various pathological events in HD. In the striatum, medium spiny GABA neurons (MSN) are preferentially degenerate while others are relatively spared. Vulnerability of specific neuronal populations within the striatum to pathological events constitutes an important hallmark of degeneration in HD. In an attempt to explain a likely mechanism of degeneration of striatal neuronal populations in HD, possible causes underlying differential vulnerability of neuronal subtypes to excitotoxic insults and neurotrophic factors are discussed in this paper.

**KEYWORDS:** NMDA, Huntington's Disease, MSN

*Corresponding Author:* Adnan Maqsood Choudhry, M.B.B.S., Division of Research & Medical Education, International Maternal and Child Health Foundation, Montreal, QC, Canada, H7S 2N5 E-mail: achoudhry@hotmail.ca

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### Introduction

Huntington's disease (HD) is a genetically dominant neurodegenerative condition characterized by progressive loss of motor and cognitive function that is caused by degeneration of selected neuronal populations within the basal ganglia and the cerebral cortex. HD is mainly driven by a genetic defect on chromosome 4 that results in an increase of repetition CAG (>39 CAG repeat to manifest disease) at the encoding site of huntingtin protein.<sup>1</sup> Profound effect in the degeneration of striatal projection neurons driven cognitive and motor impairments is the neuropathological signature of HD.<sup>2,3</sup> Based on this observation, term "selective neuronal vulnerability" is proposed by numbers of investigators (Table 1).<sup>4</sup> Overactivation of ionotropic glutamate receptors in response to endogenous or exogenous excitatory neurotransmitters via a pathological process that results in neuronal damage is well accepted as excitotoxicity phenomenon. Recent evidence suggests that excitotoxicity is one of the pathological pathways that is partly responsible for the degeneration of striatal neurons in HD.<sup>3</sup>

### Striatal histology

95% of the striatal neurons are projection neurons and only 5% are interneurons. Striatal projection neurons (also known as Golgi type I cells) are all GABAergic.

They have long axon, medium-sized cell body and spiny dendrite. Interneurons are cholinergic and morphologically distinguished by a large soma and wide dendritic arborisation.

### Differential expression of glutamate receptor subtypes and excitotoxic neurodegeneration

Glutamate is a well-known excitatory amino acid transmitter in the CNS. It activates both N-methyl-D-aspartate (NMDA) and non-NMDA ionotropic glutamate receptors. The critical role of glutamate receptors in mediating excitotoxic neuronal death in various neurodegenerative diseases is widely accepted.<sup>5-8</sup> Extensive studies show that abnormally sustained activation of NMDA receptors by glutamate can lead to prolonged increase in intracellular calcium via NMDA associated calcium channel.<sup>9</sup> Subsequently calcium dependent enzymes are activated and nitric oxide (NO) is synthesized. Neuronal nitric oxide synthase (nNOS) by itself triggers a cascade that stimulates neuronal damage. Although both medium sized spiny neurons (MSNs) and interneurons have NMDA receptors, there is an obvious difference between MSNs and interneurons in terms of expression of glutamate receptor subunits. Intrastriatal injection of agonists for NMDA (quinolinic acid) and non-NMDA (kainic acid) to animal model has shown higher vulnerability of

MSNs to glutamate-induced excitotoxicity, compared to interneurons.<sup>3,5</sup> Lack of NMDA receptor subtype NR2B/NR2A in interneurons may make these cells less susceptible to excitotoxic insults. The second group of striatal interneurons are nicotinamide adenine dinucleotide phosphate (NADP) diaphorase positive that express very few NMDA receptors and are resistant to glutamate-induced excitotoxicity. Based on these observations, differential expression of glutamate receptor subtypes in striatal neuronal populations may participate in vulnerability of these cells to excitotoxic insults.

### Selective protection of striatal neuronal subtypes by neurotrophic factors against excitotoxic insults.

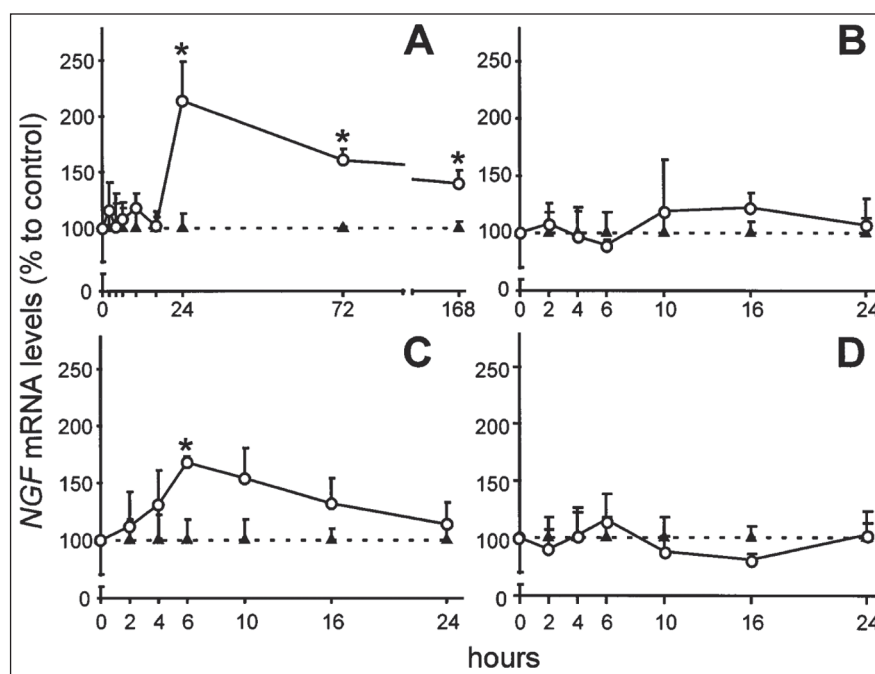
Several protective mechanisms against different types of injuries exist in central nervous system. One of the mechanisms relies on neurotrophic factors that are involved in neuroprotection of neuronal cells. Among various neurotrophic factors in the striatum, members of neurotrophin and glial cell line derived neurotrophic factor (GDNF) are well known neurotrophic factors in striatum. Neurotrophic factors selectively protect specific neuronal populations against excitotoxic insults. Through useful experimental studies, engineered cells that released neurotrophins such as brain-derived neurotrophic factor (BDNF), NT-3, GDNF and neurturin were grafted in

**Table I: Differential vulnerability of specific cell populations in HD and its relationship to morphological and biochemical characteristics**

Anatomical location	Cell type	Relative vulnerability	Morphology	Afferents	Target	NT receptors	NT	Peptides	Other molecular markers
Striatum	MSN (direct pathway)	+++	projection neuron, long axon	Cortex (Glu), SNc (DA), Thalamus (Glu)	GPe, SNr	D1, NMDA, AMPA	GABA	Substance P/ Dynorphin	DARPP-32 GAD
	MSN (indirect pathway)	+++++	projection neuron, long axon	Cortex (Glu), SNc (DA), Thalamus (Glu)	GPe	D2, NMDA, AMPA	GABA	Enkephalin	DARPP-32 GAD
	Interneurons	+	extensive dendritic network, axon projects locally	MSNs, other interneurons	MSNs, other interneurons	D2, NMDA, AMPA	Ach.	neuropeptide Y, parvalbumin	iNOS somatostatin
Cerebral Cortex	Pyramidal neurons (layers V/VI)	+++	projection neuron, long axon	Thalamus, brainstem nuclei	Striatum, brainstem, thalamus	Glu, ACh, DA, NE, 5HT	Glu	-	MAP2 CaMK
	Interneurons	+	extensive dendritic network, axon projects locally	Thalamus	Pyramidal neurons	Glu, GABA	GABA	Somatostatin, neuropeptide Y	GAD

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striatum before the intrastriatal injection of excitotoxic factors such as quinolinic acid or kainic acid. This study showed that BDNF and NT-3 equally protected both GABA/enkephalin and GABA/tachykinin positive neurons in striatum while GDNF and neurturin factors selectively protect striatal projection neurons of direct and indirect pathway, respectively. Cholinergic interneurons are only protected by GDNF.<sup>10,11</sup> Based on the result of this study, selective protection of neurotrophic factors could be due to differential vulnerability of striatal neuronal populations. Another useful experimental study showed that intrastriatal injection of quinolinic acid increased expression of nerve growth factor (NGF) mRNA level while intrastriatal injection of Kainin acid induced expression of BDNF mRNA. Quinolinic acid and Kainin acid injection did not have any effect on expression of NT-3 (Fig. 1). Interestingly, down regulation of mRNA NT-3 was observed after intrastriatal injection of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA).<sup>12</sup> This study supports the hypothesis, which suggests that activation of glutamate receptors in striatum by different excitotoxicity amino acids preferentially regulate



**Fig. 1:** Regulation of NGF mRNA levels by glutamate receptor agonists. Intrastriatal QUIN injection induced a continuous increase of NGF mRNA from 24 h until the last time examined (A). Increased levels of NGF mRNA were also observed 6 h after AMPA intrastriatal injury (C). No changes in NGF mRNA levels were obtained in KA- (B) or ACPD- (D) injected striatal. Triangles represent sham-injected striatal, whereas circle represent results from EAA injection. Values are represented as mean  $\pm$  SEM (\*P, 0.05). Neurobiology of Disease 5, 357–364 (1998).

mRNA expression of neurotrophic factors. This specific expression may explain differential vulnerability of striatal neuronal subtypes to these factors.

## Conclusion

Thus selective “vulnerability” of striatal neuronal populations to excitatory neurotransmitters and neurotrophic factors may constitute the mechanism underlying unique pattern of striatal degeneration in HD. The differential distribution of glutamate receptors and subunits in striatal neurons may alter vulnerability of striatal neuronal populations to excitotoxins. Recent studies also indicate that differential vulnerability of striatal neuronal subtypes to neurotrophic factors depends on level of expression of these factors and their receptors that are transiently up or down regulated through the activation of glutamate receptors. Since neurotrophic factors have a special characteristic to selectively protect striatal neuronal subtypes against excitotoxic insults, they may be considered as a preventative and therapeutic approach for HD.

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