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Review article

Selective basal ganglia vulnerability to energy deprivation: Experimental and clinical evidences

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ABSTRACT

The basal ganglia (BG) include structures pivotal for motor and cognitive functions. Such structures are affected in neurodegenerative disorders and toxic or ischemic insults. The peculiar vulnerability of BG to toxic and ischemic damage has been the focus of preclinical research for all over the last century. This comprehensive review collects all evidences supporting a specific susceptibility of BG to energy deprivation, highlighting the pathways through which neuronal survival is jeopardized, and the consequent clinical correlates. In particular, we addressed intrinsic and extrinsic factors participating in BG neuronal vulnerability. The terminal blood supply, the main extrinsic factor, is crucial to the low threshold for hypoxic hazard. Specific, the lack of anastomoses between second and third order branches represents the frailty of an archaic terminal network, unable to guarantee collateral supply and resistance to oxygen deprivation. In addition, BG neurons survival is jeopardized by several intrinsic molecular factors. Among them, the subunit composition of ionotropic and metabotropic glutamate receptors, the impairment of mitochondria, the deficit in neurotransmitter clearance, the poor control of intracellular calcium homeostasis and the glutamatergic-dopaminergic pro-excitotoxic interplay, all play a significant role. Intrinsic and extrinsic factors represent two faces of the same coin, producing excitotoxic damage and poor ability to deal with energy deprivation. The clinical correlates of BG vulnerability are represented by ischemic lesions, such as striatocapsular infarcts and lacunar infarcts, and local toxic-induced damage, mainly associated with energy production impairment, due to carbon monoxide, cyanide and manganese.

Abbreviations: 3-HK, 3-hydroxykynurenine; 3-NP, 3-nitropropionic acid; 6−OHDA, 6-hydroxidopamine; AADC, aromatic amino acid decarboxylase; ACA, anterior cerebral artery; ADP, adenosine-5′-diphosphate; ALDH, aldehyde dehydrogenases; ALS, amyotrophic lateral sclerosis; AMPA, a-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; AMPARs, a-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors; AR, aldehyde reductase; ATP, adenosine-5′-triphosphate; ATPases, ATP dephosphorylating enzymes; BG, basal ganglia; C, caudate; Ca^{2+}, calcium; CaMKII, calcium-calmodulin dependent protein kinase II; cAMP, cyclic adenosine 3,5 monophosphate (cAMP); ChIs, cholinergic interneurons; CN, cyanide; CNS, central nervous system; CO, carbon monoxide; CREB, cAMP-response-element binding protein; CT, computerized tomography; Cyt, cytochrome; D1 receptor, dopamine receptor type 1; D2 receptor, dopamine receptor type 2; DA, dopamine; DARPP-32, cyclic adenosine 3,5 monophosphate (cAMP)-regulated phosphoprotein of MR 32,000; DCD, delayed calcium deregulation; DNS, delayed neurological sequelae; DOPAC, 3,4-dihydroxyphenylacetic acid; DOPAL, 3,4-dihydroxyphenylacetaldehyde; DOPET, 3,4-dihydroxyphenylethanol; DWI, diffusion weighted imaging; EAA, excitatory amino acids; EAARs, excitatory amino acids receptors; EAATs, excitatory amino acids transporters; ERK 1/2, Extracellular signal–Regulated Kinases 1/2; FLAIR, fluid attenuated inversion recovery imaging; GluA(1–4), AMPAR subunit A(1–4); GluN(1, 2A, 2B, 2C, 2D, 3A, 3B), NMDAR subunits; GTS, glutamate transporting system; H_2O_2, hydrogen peroxide; HD, Huntington's disease; IC, internal capsule; IDO1, indoleamine 2,3-dioxygenase 1; KA, kainate; LIs, lacunar infarcts; LLAs, lateral lenticulostriate arteries; LOX, lypoxigenase; LTP, long term potentiation; MAGUK, membrane-associated guanylate kinases; MAO, monoamine oxidases; MAO-A, monoamine oxidases type A; MCA, middle cerebral artery; mGluR(1–8), metabotropic glutamate receptor subtype (1–8); mGluRs, metabotropic glutamate receptors; mhtt, mutant huntingtin; MLAs, medial lenticulostriate arteries; Mn, manganese; MOMP, mitochondrial outer membrane permeabilization; MPEP, 2-methyl-6-(phenylethynyl)-pyridine; MRI, magnetic resonance imaging; MSNs, medium spiny neurons; Na^+, sodium; NMDA, *N*-methyl-D-aspartate; NMDARs, *N*-methyl-D-aspartate receptors; NO, nitric oxide; O_2, oxygen; OGD, oxygen-glucose deprivation; OPTN, optineurin; Pa, pallidum; PD, Parkinson's disease; PKA, protein kinase A; PKC, protein kinase C; Pu, putamen; RHA, recurrent artery of Heubner; Rhes, Ras Homolog Enriched in Striatum; ROS, reactive oxygen species; SCIs, striato-capsular infarcts; SN, substantia nigra; SOMIs, somatostatinergic interneurons; SS, superficial siderosis; TH, tyrosine hydroxylase; THP, tetrahydropapaveroline; VMAT-2, vesicular monoaminergic transporter-2; WML, white matter lesions; YAC, yeast artificial chromosome; YAC128, yeast artificial chromosome mice model of Huntington's Disease

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1. Introduction

The basal ganglia (BG) include several sub-cortical brain structures pivotal for motor control, motor learning, cognitive function and reward (Alexander, 1986; Calabresi et al., 2014; Rosin et al., 2007). Striatum, including caudate nucleus, putamen and ventral striatum, globus pallidus, thalamus, subthalamus, and substantia nigra (SN) are all functionally considered part of the basal ganglia system. The selective degeneration of specific neuronal subtypes within these structures causes specific neurodegenerative movement disorders (Browne et al., 1997; Langston, 2006; Rampello et al., 2005; Schapira et al., 2014). The development of such diseases, all manifesting with both motor and behavioral features, derives from neurodegenerative, vascular or toxic insults able to directly and selectively interfere into the basal ganglia circuitry. The reason why basal ganglia neurons are more vulnerable than other neuronal cells has been matter of intense research in the last decades, with several mechanisms proposed to participate and lead the process of neuronal death. Among them, special attention has been drawn on specific mitochondrial complex dysfunction (Di Filippo et al., 2006; Höglinger et al., 2005; Kwong et al., 2006), poor resistance to energy deprivation (Block, 1999; Calabresi et al., 2007; Goldberg et al., 1986), on glutamate mediated excitotoxicity (Ambrosi et al., 2014; Sepers and Raymond, 2014) and on peculiar secretion of soluble factors (Zuccato et al., 2001). The purpose of this comprehensive review was to collect all the available experimental and clinical evidences of BG selective vulnerability to energy deprivation, in order to define (i) the anatomical and biochemical factors contributing to BG vulnerability to toxic agents and ischemia, and (ii) the clinical correlates of BG lesions due to the exposure to such hazards.

2. Defining basal ganglia vulnerability

Vulnerability is a dynamic concept: all cells in human body are vulnerable, each one under its own specific conditions. We might define vulnerability as the diminished capacity of a cell to detect, cope with and recover from an insult. In particular, BG neurons seem to be less endowed to survive stresses (Pisani et al., 2004). The specific vulnerability of BG resides in its molecular and anatomical complexity. BG are highly vulnerable to ischemic and toxic insults: since both these processes are based on energy deprivation and excitotoxicity, it might be hypothesized that BG have a very low resistance threshold to them (Block, 1999; Di Filippo et al., 2006; Szydlowska and Tymianski, 2010). Even though several experimental and clinical evidences supporting BG specific vulnerability to energy deprivation are available, a thorough

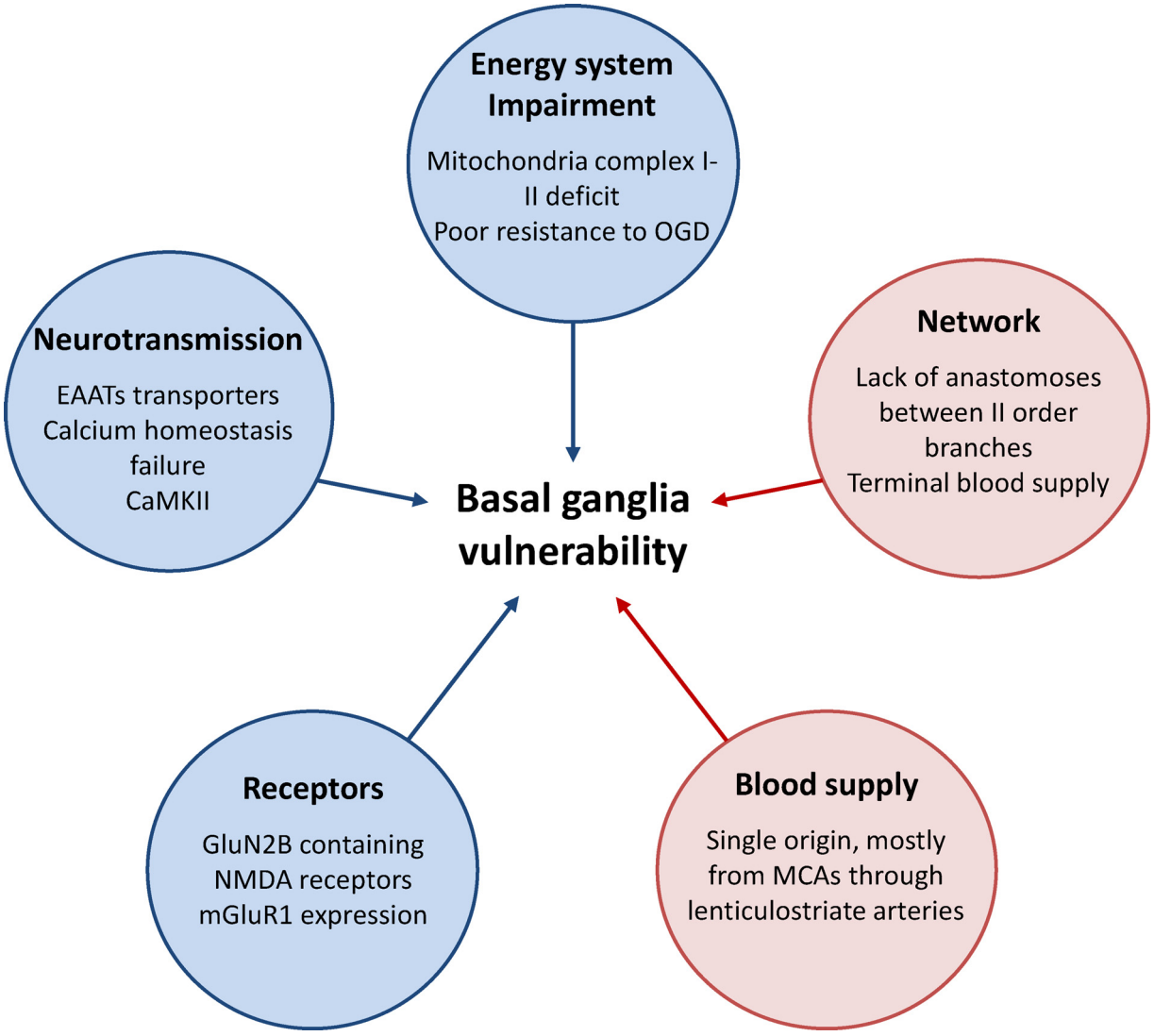

Fig. 1. Intrinsic (blue) and extrinsic (red) mechanisms participating in basal ganglia neuronal vulnerability to ischemic and toxic hazard. Legend – CaMKII: calcium-calmodulin dependent protein kinase II; EAATs: excitatory amino acid transporters; OGD: oxygen-glucose deprivation; NMDA: *N*-methyl-D-aspartate; MCA: middle cerebral artery; mGluR1: metabotropic glutamate receptor type 1.