Computational and Structural Biotechnology Journal 13 (2015) 484–491

COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL

journal homepage: www.elsevier.com/locate/csbj

Mini Review

A constraint-based modelling approach to metabolic dysfunction in Parkinson's disease

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ARTICLE INFO

Article history:
Received 12 March 2015
Received in revised form 5 August 2015
Accepted 9 August 2015
Available online 2 September 2015

Keywords:
Dopaminergic neurons
Constraint-based modelling
Metabolic reconstruction
Energy metabolism
Parkinson's disease

ABSTRACT

One of the hallmarks of sporadic Parkinson's disease is degeneration of dopaminergic neurons in the pars compacta of the substantia nigra. The aetiopathogenesis of this degeneration is still not fully understood, with dysfunction of many biochemical pathways in different subsystems suggested to be involved. Recent advances in constraint-based modelling approaches hold great potential to systematically examine the relative contribution of dysfunction in disparate pathways to dopaminergic neuronal degeneration, but few studies have employed these methods in Parkinson's disease research. Therefore, this review outlines a framework for future constraint-based modelling of dopaminergic neuronal metabolism to decipher the multi-factorial mechanisms underlying the neuronal pathology of Parkinson's disease.

Contents

1. Introduction

After Alzheimer's disease, sporadic Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting about 0.3% of the entire population, 1% of people over 60 years of age and up to 4% of those over 80 years of age [1]. In PD, neuronal populations located within several anatomical locations appear to have different susceptibility to neurodegeneration [2,3], although the classical motor symptoms of the disease result from degeneration of dopaminergic neurons (DNs) in the substantia nigra pars compacta [1,3]. Despite intensive research, the cause and biochemical mechanisms of dopaminergic neuronal death in PD are incompletely understood. Proteostasis, oxidative stress, mitochondrial dysfunction, excitotoxicity, neuroinflammation and more recently gut microbial dysbiosis have all been associated with PD [4–8]. However, the relationship between these processes is poorly understood, especially with regard to the causes, effects and the relative importance of each dysregulated process in PD. This

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http://dx.doi.org/10.1016/j.csbj.2015.08.002

review summarises some molecular pathological features of selective dopaminergic neuronal degeneration, discusses recent advances in systems-level computational approaches, and presents a framework based on several key methods of constraint-based modelling that we envisage will help unravel aetiopathogenesis of PD.

2. Aspects of molecular pathogenesis in Parkinson's disease

Substantia nigra DNs consume a large amount of energy to maintain a tonic electrophysiological activity in their axonal terminals within the striatum, making these cells especially vulnerable to any impairment of energy metabolism [9]. In energy metabolism, oxidisation of nutrients (e.g., glucose) is kinetically coupled to reduction of cofactors (e.g., NAD^+ reduced to NADH, prosthetic group FAD reduced to FADH_2, $NADP^+$ reduced to NADPH). In turn, oxidation of reduced cofactors is kinetically coupled to generation of energy currency metabolites (e.g., ATP, GTP). Energy currency metabolites are used to drive otherwise thermodynamically unfavourable reactions that are required for maintenance of normal cellular functions, such as scavenging of reactive oxidative species (ROS), or in the case of DNs the synthesis, release and reuptake of dopamine [10]. Oxidisation of reduced cofactors can also be used to directly to drive certain biosynthesis reactions.

Modulation of NAD^+-dependent enzymes is currently being explored to treat neurological illnesses, e.g., the key NAD^+-dependent enzymes SIRT1 and SIRT2, which have been associated with the α-synuclein aggregation process in PD [11]. Furthermore, in a previous study, a parenteral application of NADH in PD patients resulted in increased endogenous L-DOPA (L-3,4-dihydroxyphenylalanine) biosynthesis and alleviation of the disease motor symptoms [12].

Moreover, degenerating DNs are accompanied by an increased iron accumulation [13] and also excrete neuromelanin (NM) [14] and ROS, which are responsible for microglia activation. These factors contribute to excessive neuroinflammation, which may exacerbate neuronal death [5,15]. Recent evidence has also shown the existence of synergy between neuroinflammation in PD and gene products linked to Parkinsonian phenotypes (such as α-synuclein, parkin, Nurr1, and regulator of G-protein signalling-10) [16]. A previous study using a PD mouse model found that the activation of glial cells can induce the expression of cyclooxygenase-2 (COX-2) in DNs, enhancing the susceptibility of DNs to degeneration [17].

3. Computational systems approaches to dopaminergic neuronal metabolism

Elucidation of the molecular aetiopathogenesis of PD requires an interdisciplinary systems approach [18] to understand how dysfunctions of disparate pathways interact to result in neurodegeneration (Fig. 1). A systems approach consists of an iterative cycle of mathematical model formulation, computational modelling and quantitative experimental measurements. Mathematical and computational models are formal representations of biochemical knowledge that are used to propose hypotheses, design experiments and interpret experimental results. Quantitative experimental measurements are used to test hypotheses generated by a model and also generate data used to refine the content of a model.

An ultimate aim of the application of a systems approach to PD would be to be able to make non-trivial predictions of DN reactions, where quantitative modulation would either significantly imbalance normal DN energy supply, or re-balance DN energy supply in DNs generated from induced pluripotent cells derived from PD patients. At the core of this approach is an effort to reconstruct a state-of-the-art metabolic network of substantia nigra DNs, and then to apply computational modelling for generating experimentally testable hypotheses as to the aetiopathogenic nature of PD.

Network reconstruction is a prerequisite for computational modelling. A high-quality reconstruction is built from a variety of biological knowledge sources such as genome annotations, metabolic databases (e.g., KEGG and BRENDA) and biochemical literature manually curated in a quality-controlled manner [19]. These genome-scale network reconstructions provide a detailed and self-consistent representation of biochemical reaction networks and provide a basis for computation of biochemically feasible functional states using computational modelling, e.g., constraint-based modelling.

Constraint-based modelling is a scalable computational modelling approach widely used for prediction of physicochemically and biochemically feasible steady-state metabolic fluxes (reaction rates) in living

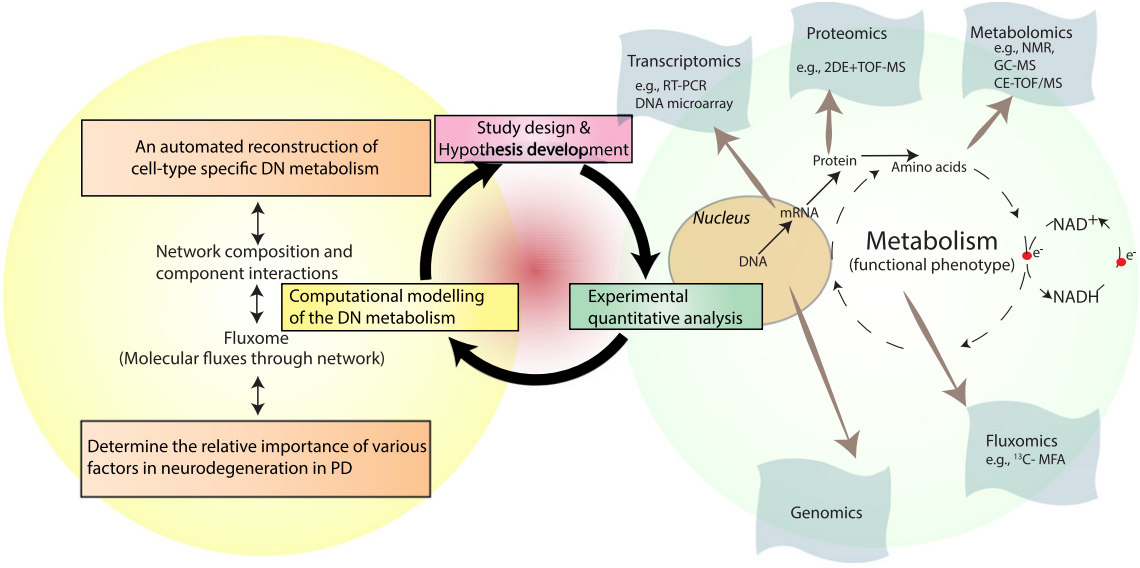

Fig. 1. The conceptual scheme of the constraint-based modelling approach to decipher Parkinson' disease. Fluxomics quantifies the reaction rates that describe the time-dependent passage of metabolites through reactions; exometabolomics measures the abundance of primary and secondary metabolites in the extracellular environment. The modelling tasks that can be conducted by the constraint-based modelling methods are indicated by the light-yellow halo, whereas quantitative analysis that needs to be validated by experimental tools are indicated by the light-green halo. RT-PCR, reverse transcription-polymerase chain reaction; DN, dopaminergic neuron. NMR, nuclear magnetic resonance; GC–MS, gas chromatography–mass spectrometry; CE-TOFMS, capillary electrophoresis time-of-flight mass spectrometry; 2DE, two-dimensional gel electrophoresis; 13C-MFA, ^{13}C metabolic flux analysis.