Chapter 2
Modelling and Simulation of Brain Energy Metabolism: Energy and Parkinson's Disease

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Abstract The brain is the most energy intensive organ in the human body, so it is to be expected that weaknesses in brain energy metabolism could be a potential factor in neurodegenerative conditions. This is the starting point for a systems biology study of how known Parkinson's disease (PD) risks can weaken brain energy metabolism and contribute to the preconditions for disease. We begin by describing PD as a multifactorial condition in which energy deficits form a common denominator for known risk factors. This is followed by a description of a mathematical model of brain energy metabolism, and its structural and dynamic properties. Simulations of the model are then used to illustrate how external risk factors, plus structural and dynamic weaknesses in neural energy supplies, particularly affect neurons most vulnerable to PD damage. Taken together, these issues form the basis of an energy-deficit theory for how the preconditions for PD are formed.

Introduction

For the majority of Parkinson's disease (PD) sufferers, the cause of their condition is unknown. This idiopathic/sporadic form of PD represents around 90% of known occurrences, with the balance being composed of the familial form, where there is a clear genetic mechanism [1]. The causes of idiopathic/sporadic PD are not a complete mystery. It is, for example, known that certain risk factors will raise the likelihood of developing idiopathic/sporadic PD. These risks include advanced age, exposure to certain toxins, head trauma, plus possible other factors [2, 3].

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It is generally assumed that risk factors accumulate in some unknown way to create preconditions in which PD can develop. The aim in this chapter is to consider how this happens. In particular, we describe the development of an in silico framework for the study of PD in the form of a mathematical model of brain energy metabolism. This model is then used to probe underlying causal mechanisms for PD, and in particular the search for a common causal denominator that unifies the diverse set of known risks.

PD Is a Multifactorial Condition

PD is a heterogeneous condition that manifests in a variety of ways and with various symptoms. This continues throughout the course of the disease, with the rate and nature of its progress varying from one sufferer to another. Variability, considered with other issues [4, 5], has led to the consensus view that there is no single causal mechanism for PD and that there are a variety issues (risk factors) that contribute to PD in, as yet, undefined multifactorial ways [6].

The existence of a set of possible risk factors for PD presents an opportunity for systems biology. Specifically, if systems biologists can construct a suitable mathematical model it will be possible to apply a computer implementation of the model to systematically investigate in silico the many combinatorial and temporal variations that multifactorial problems present. Based on such a systems biology approach, the viewpoint put forward in this chapter is that (1) individual PD risk factors, if severe, may work alone, or more usually, in multifactorial combination, (2) PD risks factors are "causal" only in the sense that they create the preconditions for pathogenesis to be initiated, and (3) there is a common denominator for all non-genetic PD risk factors in the form of cumulative neuronal energy deficits.

PD Risk Factors

The single most important of risk factor in idiopathic PD is age (see Chap. 3). The statistical risk of developing PD rises significantly as we get older, increasing particularly after the age of 60 years, but decreasing again in extreme old age [7]. In addition to age, there is also strong evidence of risks due to exposure to certain chemicals used in the workplace. This risk associates particularly with toxins associated with land workers [8] and certain industries [9, 10]. How such toxins contribute to PD was revealed by the case of the frozen addicts of California [11]. This concerned the incidence of severe Parkinsonian symptoms in young drug addicts who had injected drugs that include a neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Subsequent research showed that MPTP creates Parkinsonian symptoms through damage to neuronal mitochondria.

A third risk factor for PD, or at least PD symptoms, is severe head injury (head trauma, see Chap. 1). While this is generally accepted as a risk, it is not supported by strong statistical evidence. In fact, the number of PD sufferers that are known to have experienced head trauma is relatively small, so that it is difficult to gather sufficient evidence to be statistically convincing. Nonetheless, in the case of severe head injury, and in sports that involve repeated violent head impact, there is strong circumstantial evidence. In boxing, Muhammad Ali is the most famous case, with further examples in other high-impact sports. Outside of sport, other sufferers have reported incidents in their formative years during which they received severe blows to the head.

A life-course factor that influences PD risk in a beneficial way is physical fitness. In particular, there is statistical evidence that vigorous physical exercise, particularly in youth, has a protective effect [12]. Unconnected with this protective factor, a number of genes have been implicated in familial PD [1]. However, as suggested by the case of the Ohio Kindred, a high level of genetic damage appears to be required in order to trigger familial PD [13]. An inference drawn from this is that limited irregularity in "PD genes" be tolerated but that they can provide a background level of predisposition, upon which the various risk factors then build [14].

Energy as a Common Denominator

There is a connection between the major risk factor—advancing age—and a decline in energy metabolism. Specifically, the efficiency of the cerebral energy metabolism, and the general effectiveness with which our bodies utilise glucose, reduces with age [15, 16]. The decline in energy generation and utilisation takes place gradually over a person's lifetime (Chap. 3). This suggests a linkage between an increased chance of PD in an ageing brain, and the declining effectiveness of brain energy metabolism in the elderly. On the reverse side, the apparent protective influence of vigorous exercise [12] could be to slow down the rate of metabolic decline—keeping the energy metabolism "on its toes", so to speak.

Age is not the only risk factor to have an energy link. Revisiting other factors—external toxins and head trauma—shows that they too are associated with a compromised brain energy metabolism. In particular, toxins linked to PD are known to selectively damage the energy generating mechanisms of mitochondria [10, 17], weakening their ability to maintain neural ATP (adenosine triphosphate) levels. In addition, damage to the brain's supporting structures of capillary and astrocytic systems may reduce the effectiveness of energy metabolism. As illustrated later, astrocytic damage in particular may compromise transient energy supplies during neuronal signalling.

So far, we have discussed the "supply-side" of energy in the brain. Now, we consider the "demand-side" argument. As far as it is known, neurons are the only

cells to experience Parkinsonian damage. So to understand why energy should be a factor in PD, we consider why neurons are special from an energy demand perspective:

Neurons work harder than other cells: Between 10 and 20 times harder in fact, with most of the additional energy requirement being needed to fuel neural signalling [18]. Their higher work rate implies that neurons would be more susceptible to failure if their energy metabolism were to be deficient.

Substantia nigra neurons work the hardest of all: Dopaminergic neurons in the *substantia nigra* are the most vulnerable to PD damage. And as explained in Chap. 1 and [19], they are, by a very large margin, the most demanding neurons in terms of the energy requirement.

Substantia nigra neurons signal differently: *Substantia nigra* neurons also have a continuous "pace-making" feature and use calcium to facilitate this signalling. As discussed in Chaps. 4 and 5, these two factors further amplify the energy load on *SN* neurons.

Long axons need more energy: Neurons with long and/or lightly protected axons have also been found to be more vulnerable to Parkinsonian damage [20]. This provides another connection between vulnerability and energy requirements, since the longer the axon, the greater the amount of energy needed to perform signalling [21].

Brain Energy Metabolism as a Framework for the Systems Biology of PD

The mathematical modelling of physical systems can be interpreted as the analysis of energy flows within the system [22]. This involves partitioning the system into a central energy supply compartment, plus a set of modules that draw down energy from the supply and use it to perform their function within the system. The same approach can be applied to modelling living systems and, in the current context, to the modelling of PD [23]. Proceeding in this vein, the brain energy metabolism forms the central energy-supply model compartment, while the various cellular and metabolic processes that give neurons their function are the modules that attach to the central compartment.

In the modelling of a particular neurological disease, only those cellular modules implicated in the specific condition need be considered. Thus, for a mathematical model of PD, we would have a central brain energy metabolism model as the framework, and the cellular functions implicated with PD attached to it, as indicated in Fig. 2.1. Because of the strong implication of energy in PD, this chapter concentrates on the construction of a mathematical model of brain energy metabolism. The role of cellular processes implicated in PD is discussed in subsequent chapters of this volume.

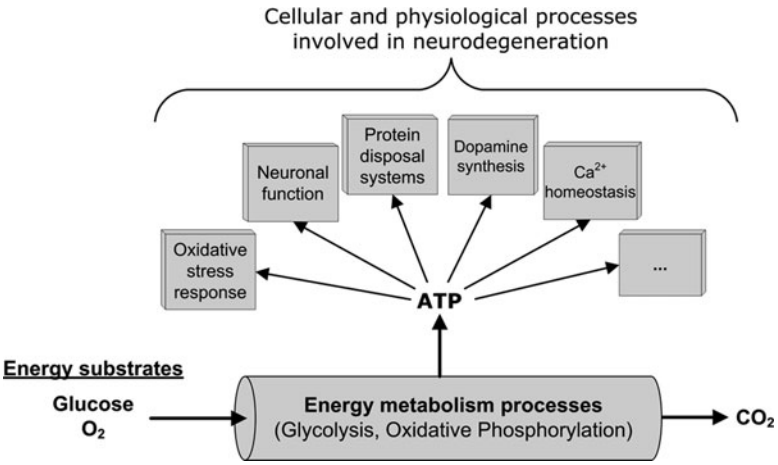

Fig. 2.1 Brain energy metabolism as a modelling framework for neurodegenerative disease. The brain energy metabolism forms a central modelling structure with modules representing cellular functions associated with a particular condition (in this case PD) connected to it by their dependence upon ATP supplies; cross-linkages between modules are used to model interdependence of cellular functions

Brain Energy Metabolism Modelling

Following work by Aubert and co-workers [24], we take a compartmental view, with four main compartments: brain capillaries, neurons, astrocytes and the extracellular space. In the form described here, the brain energy metabolism model is for a generic region within a neuron, with no special features that would associate it with a particular neural function, structural form, or spatial location. A more complete model of PD would recognise the specifically different features of vulnerable neurons, e.g. calcium facilitated signalling (see Chaps. 4 and 5), dopamine metabolism (see Chap. 8), take account of morphological variations (e.g. Chap. 1) and other spatial factors in PD. Since the model is designed to be extended, such features can be accommodated subsequently by modification of model parameters or by the incorporation of new modules as suggested in Fig. 2.1.

The role of astrocytes in brain energy metabolism was suggested in [25, 26] through the proposal for an astrocyte-neuron lactate shuttle (ANLS), whereby lactate from astrocytes supports the neuronal ATP system. Although the ANLS theory is not universally endorsed, the general consensus is that astrocytes play a role in energy metabolism by their release of lactate. This consensus is supported by modelling studies in [27, 28] and experimental observation of extracellular lactate levels during astrocytic blockade, (see Chap. 6 and Fig. 2.3). Later, we comment on the ANLS theory through a developmental argument for the existence of astrocyte support for neuronal ATP.

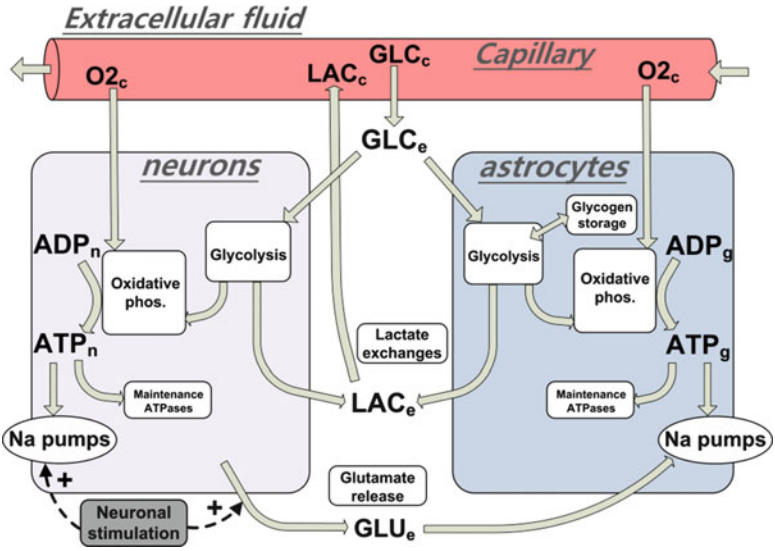

Fig. 2.2 The compartmental structure of the brain energy metabolism model. The model represents a general area within a neuron. Energy substrates glucose and oxygen (GLC, O_2) from the capillary compartment enter the neuronal compartment and astrocyte compartments via the extracellular compartment. There is an additional path for energy substrates directly from capillaries to astrocytes

Brain Energy Metabolism Model

The model outlined here was first developed for the study of neurodegenerative conditions in general [29]. Amongst other features, it includes the representation of the astrocyte–neuron coordination by modelling neuronal and astrocytic activity as a coordinated neurotransmitter cycling (the glutamate loop). A further important feature is the description of astrocytic glycogen dynamics as an astrocytic storage capability. Finally, the model of the central energy metabolism is extended to include a more detailed representation of glycolysis and mitochondrial regulation.

A complete description [29] of the model involves 12 independent states for neurons, 13 for astrocytes, 3 extracellular states and 4 capillary states. In total, 42 kinetic equations are used to describe the metabolic system, and the model has 63 kinetic parameters (reaction constants, maximum reaction rates, affinity constants and regulation parameters). The kinetic rates included in the model also use 27 physical constants (volumes fractions, arterial concentrations, electrochemical constants, etc.). These constants are assumed to be known and representative of the system (see [24, 30], with further details in the CellML metabolism directory).

In the following section, we restrict ourselves to the model design and features as they relate to subsequent discussions of energy and PD. The model structure is

illustrated in the schematic view of Fig. 2.2, and its main characteristics are as follows:

Cerebral compartments and exchange systems
There are four main compartments in the model: neurons (variables indexed "n"), astrocytes (variables indexed "g"), capillaries (variables indexed "c") and extracellular space (variables indexed "e"). Glucose (GLC) is transferred from capillaries to neurons and astrocytes via the extracellular space. In addition, and because of the intimate contact between astrocytes and capillaries, there is an additional direct transfer pathway of GLC. Glucose transport is described by facilitated diffusion, while LAC transport is modelled by the same mechanism, with the exception that chemical gradients are arranged to favour release of LAC, instead of uptake as for GLC. The dynamics of Oxygen (O_2) and carbon dioxide (CO_2) in the extracellular space are ignored so that transport of gaseous species between capillaries and tissue is direct.

Central energy metabolism
In Fig. 2.2, the central energy metabolism of both neurons and astrocytes consists of glucose entering the cells, from where it is converted by glycolysis to pyruvate (PYR). This process is modelled in the sequence: adenosine triphosphate (ATP) is consumed by the hexokinase (HK) and phosphofructokinase (PFK). Glyceraldehyde-3-P (GAP) produced from the PFK reaction is then converted to phosphoenolpyruvate (PEP), with nicotinamide dinucleotide (NADH) regeneration from NAD and, finally, the production of PYR from PEP by the pyruvate kinase. Pyruvate produced by glycolysis can either be converted to LAC, or oxidized in the mitochondria (v_{mito}) to regenerate ATP from ADP (adenosine diphosphate).

The regulation mechanisms and reactions for energy metabolism used in the model are modified forms of those described in [24, 30] and [31]. The modifications involved the addition of inhibition of mitochondrial activity at high ATP–ADP ratio [30] and the removal of secondary activation of mitochondrial activity (model validation tests showed it to be unnecessary). Thus, the model describes mitochondrial regulation from the availability of PYR, O_2 and energetic requirements of the tissue. Energetic metabolism in neurons and astrocytes is buffered by phosphocreatine (PCr), which is used to regenerate ATP during short-term abrupt increases in energy demand. Adenosine monophosphate (AMP) equilibrium with ADP and ATP through the adenylate kinase reaction is neglected. Using kinetic parameters from the literature for adenylate kinase, it was observed that AMP dynamics were negligible in the conditions of this study (simulations results not shown).

Neuronal stimulation system and the glutamate loop
The major "sink" for energy metabolism is the maintenance of ionic gradient in neurons and astrocytes through sodium pumping (Na pumps in Fig. 2.2). The dynamics of sodium are considered in a way that allows the description of the tissue energetic "load" both in resting conditions (Na-ATPases pumps working to maintain Na gradient) and during stimulation (increased Na inflow in neurons). The stimulation of neurons is modelled as a base stimulation rate (flow of Na after neuronal habituation) and a spiking at the onset of stimulation.

As described earlier, an important phenomenon in the ANLS view of brain physiology is the coordination of neuronal and astrocytic response during stimulation. Such a coordination mechanism is implemented through the uptake of glutamate (GLU) by astrocytes (with Na co-transport) after neuronal stimulation. Subsequent to the initial ANLS proposal, the GLU loop has been assessed through NMR measurements [32, 33], with the quantitative importance of the glutamate loop being emphasised in [34]. The model represents the physiological response of the cerebral tissue in the glutamate loop through a series of reactions. As shown in Fig. 2.2, the loop is described by: (1) the release of GLU by neurons, (2) cleaning of extracellular space by astrocytes (with Na co-transport) and (3) non-stimulatory recycling of GLU from astrocytes back to neurons. The GLU loop model is simplified by neglecting the dynamics of glutamine (a non-stimulatory intermediate in the transfer from astrocytes to neurons). This enables the conversion of GLU to glutamine in astrocytes, with transfer to neurons and reconversion to GLU, to be modelled as one reaction.

The GLU loop activates astrocytic metabolism through two mechanisms. First, Na pumps are activated to maintain the Na gradient in the astrocytes, consuming ATP in the process. Second, the conversion of GLU to glutamine requires 1 molecule of ATP per molecule of GLU processed. Thus, the GLU loop allows a proportional activation of astrocytic and neuronal metabolism, with an increase in ATP consumption in both cell types. This increase in energy demand directly activates the PFK through an activation-inhibition kinetic for ATP and potentially the whole glycolytic flux. An increase in the mitochondrial activity is also expected (direct activation by ADP and reduced inhibition by ATP). Including the glutamate loop in this way allows the astrocytes–neurons physiological coordination to be described by a physiologically realistic mechanism.

Glycogen metabolism

The inclusion of astrocytic glycogen (GLY) storage in the model (see Fig. 2.2) was a key mechanism in enabling the model to reproduce the variations of GLC and LAC observed in vivo (see Chap. 6). It proved possible to model GLY dynamics with two reactions: synthesis and breakdown. Synthesis of GLY occurs during "rest" periods, whereas breakdown is activated by "work" periods, e.g. neuronal stimulation periods (induced by noradrenaline). This mechanism allowed an additional input of energy substrate during high-energy demand periods, and proved critical during model validation against experimental data. The modelling of GLY dynamics would however benefit from further analysis of the dynamics of GLC and O_2 consumption and uncoupling phenomenon (GLY is a buffer between the entering GLC flux and its mitochondrial oxidation). In particular, an increase in energy substrate inflow is required to explain how LAC and GLC concentrations could both be higher than their baseline values for a long period of time after neural stimulation. The transfer of GLC between capillary and extracellular space, even though it constitutes the major GLC inflow to the tissue, does not show sufficient variations to explain the GLC profile.

Brain Energy Metabolism: In Silico and In Vivo

Model Calibration

Values of parameters, coefficients and physical constant were, where possible, taken from the literature. Volumes fractions, resting steady-states values, sodium transport parameters and CBF values were considered to be the same as reported in [24] and [30]. Likewise, in calibration routines [35], the initial values for parameters were taken mainly from [24], with the GLU coordination loop parameters initialised to produce a cycling of GLU consistent with values reported in [34] and [30]. Additional parameters on LAC transport and regulation (affinity constants and maximum reaction rates) were obtained from data in [36]. The parameters of glucose transport kinetics were based on glucose transport literature [37]. Literature information on kinetic parameters also ensured that the model operated within a realistic physiological range (when measured in terms of concentrations and fluxes). A second-stage of calibration involved using in vivo time-course histories of GLC and LAC measurements during perturbations experiments with animals. These real-time measurements, as described in Chap. 6, provided time course calibration data for dynamic tuning of the model to the extracellular changes that take place in cerebral metabolism during neural stimulation.

Calibration was performed using in vivo measurements of extracellular cerebral GLC and LAC from data obtained during active neurological stimulation [38, 39]. These time histories were used in the Systems Biology Toolbox [35] to search for model parameter sets that optimally matched the model dynamical performance with the observed time course information in [38, 39]. Examples of the source in vivo data for GLC and LAC in normal conditions, plus the corresponding in silico data are compared in Fig. 2.3b and 3c.

Validation, Prediction and Visualisation

Calibration of the model ensures that it is able to reproduce in vivo data. However, to be acceptable, the model also required validation. This was done by testing its capacity to predict observed behaviour that is outside of its calibration range: that is to say by comparing model outputs with independent experimental data collected in modes of behaviour not included in the calibration. For this, we used the model to predict, in silico, the variations in extracellular GLC and LAC when the astrocytic coupling is reduced using propranolol. Figure 2.3e, f compares predictions with the corresponding independent in vivo measurement of GLC and LAC where astrocyte action is reduced [39]. The two diagrams show how the model predicts

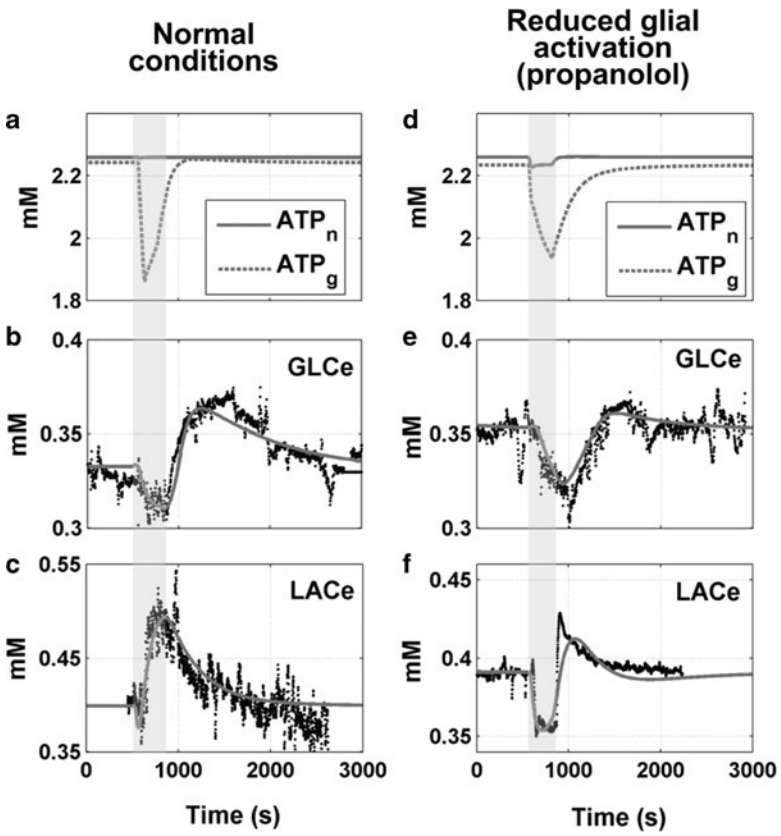

Fig. 2.3 Calibration and validation of the brain energy metabolism model. Plots (**a**, **d**) in row 1 show variations in intracellular ATP variables not measureable in vivo. (**b**, **c**) Calibration data for extracellular GLC and LAC. (**e**, **f**) Validation data obtained by comparing results with reduced astrocytic activity in vivo with in silico predictions

a drop in extracellular LAC that is later observed in vivo. This result is significant: (1) at a fundamental level it supports the ANLS theory and (2) for PD it has implications for head trauma as a risk factor. In particular, it implies that any damage to neuron–astrocyte coordination, such as might be caused by head trauma, will reduce the astrocytic support of neuronal ATP during signalling. Thus, we would expect that head trauma, in addition to direct damage to brain capillaries and neuronal structures mentioned in Chap. 1, would also induce additional energy-stress through astrocyte damage.

The ability to make real-time measurement of dynamic variations inside cells of the living brain could help unlock the secrets of neurodegeneration. In silico tools, such as the brain energy metabolism model, offer hope in this direction. Specifically, in addition to prediction of extracellular variables, the model enables variations in intracellular fluxes to be visualised. For example, Fig. 2.3a, d show

visualisations of neuronal ATP levels. As discussed elsewhere in this volume, such visualisations using in silico models may offer insights into otherwise "hidden" cellular mechanisms. Notice in particular that with astrocytic action reduced (Fig. 2.3b), the neuronal ATP level is temporarily reduced during stimulation.

Systems Properties of Brain Energy Metabolism

The act of mathematical modelling forces a strict discipline on the systems biologist. In a mathematical model, each reaction must be defined in quantitative terms, and related to other reactions involved in the model in a consistent way. A benefit of this discipline is that core systems properties are revealed in useful ways. In the brain energy metabolism model, two such properties are relevant to PD—both concern the consistent supply of neuronal ATP as determined by the mechanisms that control and regulate the brain energy metabolism. Details of brain energy metabolism control are given in [40]; here, we review points that relate to PD.

ATP Regulation

As illustrated in Fig. 2.4, the regulation of ATP is provided by a combination of two feedback loops. The outer feedback loop is a legacy from the control of glycolysis in simple cells and would, on its own, provide relatively poor control [41]. However, the quality of control is greatly strengthened by the second (inner) feedback loop, and the two together ensure ATP supplies are regulated to a consistent and constant homeostatic level during the steady "rest" state, and during slow changes in activity.

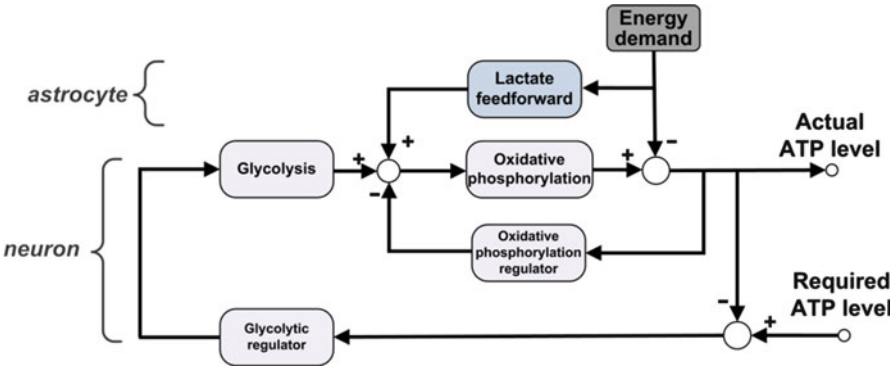

Fig. 2.4 Energy regulation and control structure for brain energy metabolism. Two feedback loops regulate the ATP supplies for the steady homeostatic state. The lactate feedforward loop supplements oxidative phosphorylation during stimulation and enables the neuron to create ATP supplies during rapid, transient, energy demands

This suffices for most human cell types, but good steady-state regulation is not sufficient in neurons: the energy demands of signalling requires transient bursts of extra ATP [42], and these, in turn, requires the brain energy metabolism to accommodate rapid changes in ATP levels. Unfortunately the two feedback loops cannot respond fast enough, and instead the transient demands of energy are met by the fast feedforward lactate loop shown in Fig. 2.4. This coordinated release of astrocytic lactate, supports the specific element of the overall neuronal energy budget associated with rapid transient ATP demands. The implications of this for PD can be seen from the following systems view.

Astrocyte Feedforward

Within the model, astrocytes are activated during signalling by neuronal release of neurotransmitters during signalling, with coordination provided by the uptake by glial cells (astrocytes in particular) of excess neurotransmitters. In order to do this, astrocytes draw upon the efficient glycogen storage mechanism and consequently undergo an increase in glycolytic rate and LAC production. Such increases in LAC have been observed experimentally during high activity periods in the brain [43, 44] and are a feature of our model response (e.g. Fig. 2.3c). The use of a secondary system (e.g. astrocytes) to produce a supplementary energy substrate (LAC) for the main functional system (neuron) is a biological equivalent of feedforward control structures used to regulate technological processes during periods of sudden large demands [45]. In such processes, feedforward is designed to give an early and rapid response to a change that cannot be met quickly enough through the feedback pathway. In brain energy metabolism, the feedback pathway passes through a number of intermediate states that, particularly in glycolysis, incurs a significant time delay. For the neuron, the use of lactate feedforward is a natural cooperative development that short-circuits this delay as follows: the increase in energy loading (i.e. increase in neurotransmitter circulation) is forwarded to astrocytes. The astrocytes respond by drawing upon their glycogen store to produce LAC. In its turn, the higher available LAC concentration then favours neuronal uptake, oxidation in neurons and consequent increase of ATP just when it is required for signalling.

The feedforward mechanism is independent of feedback action within neuronal metabolism (i.e. LAC will increase regardless of ATP levels in neurons) and enables the feedforward loop to bypass the time delays in glycolysis. In classical control, this type of controller can be finely tuned to reject disturbances on the system. Again, analogies for this tuning are found in the systems biology literature, for example in the perfect adaptation system presented in [46].

Figure 2.3c demonstrates, in vivo and in silico, the extracellular LAC variations with the feedforward LAC mechanism. The change in energy demand here is relatively small (25%) as it is reported that the basal metabolic rate in neurons is relatively high (i.e. as much as 90% of the active rate). This corresponds with observations, during physiological stimulations, of a maximum of 20–25% increase in energy demand.

The Role of Glycogen Storage

Astrocytic feedforward works because of glycogen storage. In particular, the additional inflow during stimulation is assumed to be coming from an activation of glycogen breakdown by a molecular signal (noradrenaline) that is known to be involved in sensory response. The amplitude of that GLY breakdown flux during stimulation was found to be of the order of 2×10^{-3} mMol s^{-1}.

The increase in GLY breakdown allows astrocytes to switch from a pure GLC usage to a mix of GLC and GLY usage. The comparison of hexokinase rate and glycogen breakdown in astrocytes provides a clear explanation for the observed triphasic behaviour for GLC. First, at the onset of stimulation, the activation of glycolysis in astrocytes induces an increase in the hexokinase rate that explains the rapid decline in GLC concentration. Then, after a delay, the noradrenaline "signal" induces GLY breakdown, which supplies the excess GLC needed in astrocytes. Thus, the hexokinase rate returns to its steady-state value as soon as the GLY breakdown is initiated, which stabilises the extracellular GLC concentration. After stimulation ends, the noradrenaline signal still activates GLY breakdown, this induces an increase in G6P, which in turn inhibits hexokinase, and results in a fast increase in extracellular GLC.

Using the GLY store during high demand periods allows the cerebral tissue to meet its increased energy requirements with minimal changes in GLC transport from the capillaries. This smoothing action allows GLC level to be maintained in the cerebral environment during stimulation, a factor that is critical for neuronal glycolysis (neurons do not accumulate GLY). The described GLY breakdown (2×10^{-3} mMol s^{-1} for 400 s) would lead to a dip of ~0.8 mMol in astrocytic GLY concentration. This corresponds with the current literature on GLY levels in astrocytes that report GLY concentrations in astrocytes in the range of 1.4–4.2 mMol (adjusted for units consistency) [47]. The model also shows that the GLY pool is easily replenished in resting conditions, thus bringing an overall balance between high and low activity periods (simulations not shown). GLY is thus considered here not as an "infinite" substrate pool, but rather as a dynamic energy reserve that the cerebral tissue can draw upon to buffer its "energy budget" between low and high demand periods.

Simulating PD Risk Factors

Earlier we described how the neurons most vulnerable to PD damage also have the highest energy requirements. Reference was made to the morphological evidence given in Chap. 1, and further in silico evidence from the issues associated with calcium-facilitated signalling (Chaps. 4 and 5). It was further explained that the known PD risk factors each involve impairment of neuronal ATP availability. This was then used to claim energy deficits as the common denominator in the risk

factors that create preconditions for PD. In this section, we use simulations of the brain energy metabolism model to explore this claim. In particular, we demonstrate the influence on neuronal ATP of individual PD risk factors: age, toxin exposure and head trauma as they might be expected to gradually develop over a number of years.

The three risk factors are modelled as follows. (1) *Toxins*: the cumulative impact of a prolonged low-level neurotoxic exposure is simulated by a linear decline in mitochondrial efficiency (from 100 to 50%) over a 10-year period. (2) *Age*: the gradual decline of metabolism with age is represented by a linear reduction (from 100 to 75%) in the efficiency of glucose transport capacity over the same period. (3) *Head trauma*: the potential influence of head trauma is modelled as reduced astrocytic support of brain energy metabolism, and is simulated by a linear reduction in astrocytic activity, (from 100 to 35%) over the same simulation period. The simulations (Fig. 2.5) are in two parts: row two of the figure shows how risk factors influence the regulation of neuronal ATP during the steady "rest" state of the brain. The simulations shown in row three highlight the impact of transient ATP dynamics during neuronal signalling.

Steady-State ATP Regulation

Consider first the steady "rest" state ATP during the gradual metabolic decline associated with age and other risk factors such as head trauma. Figure 2.5 shows the individual application of three known PD related factors: (1) loss of mitochondrial complex I efficiency (Fig. 2.5a), (2) lower glucose transport capacity (Fig. 2.5b), and (3) loss of neuron–astrocyte metabolic interactions (Fig. 2.5c). The key point from these three plots (second row in Fig. 2.5) is that the ATP regulation system (e.g. the two feedback loops in Fig. 2.4) is highly effective maintaining a constant level of ATP even under significant deterioration in brain energy metabolism. Simulations of combinations of risk factors (not shown) indicate that the steady-state regulatory system remains robust during combinations of risk, but is more strongly challenged and fails earlier as more risks are imposed. This in silico result suggests an additive effect when combinations of risk are applied. Moreover, the particular combination of risk is not important since all risks reduce energy availability: it is the number and severity of risks that is important.

Transient ATP Control During Signalling

The two feedback loops in the brain energy metabolism prove themselves robustly capable to supply steady-state ATP requirements. Even with combinations of risk factors, the steady ATP levels maintain a good degree of resilience. However, when

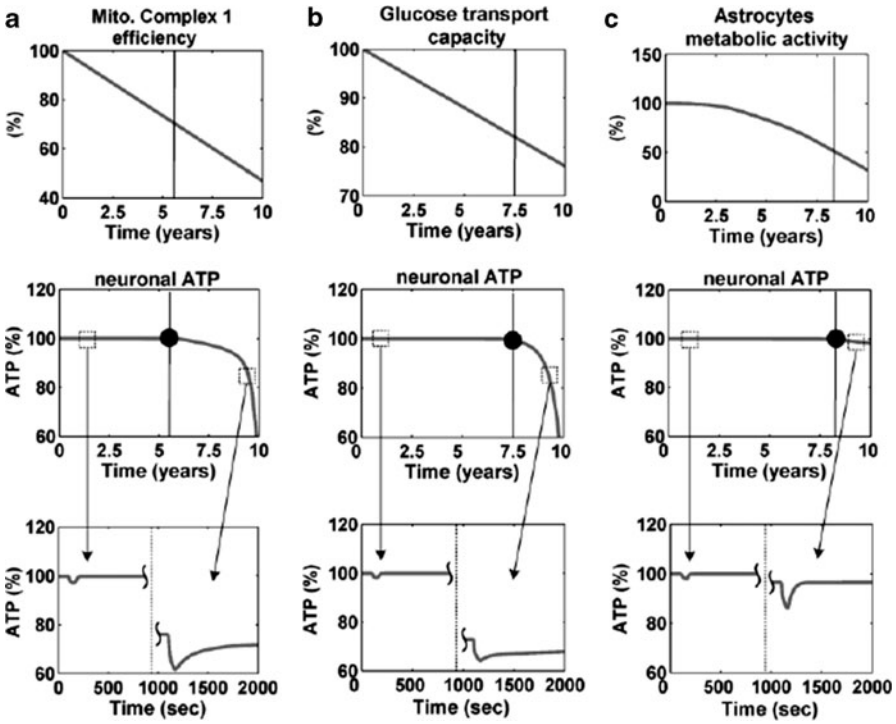

Fig. 2.5 Steady "rest" state regulation and transient control of ATP in brain energy metabolism. Deterioration of energy regulation as PD risks factors grow with time: (**a**) loss of mitochondrial Complex I efficiency; (**b**) lower glucose (GLC) transport; and (**c**) loss of astrocytes connectivity from head trauma. The *second row* shows long term dynamics of ATP (as a % of healthy steady state). The *third row* shows excerpts of short terms dynamics (1-min stimulation) before and after energy regulation is compromised

bursts of energy demand for signalling are added to the rest energy demand, the story changes and the neuronal ATP supplies are less able to respond to demand with sufficient speed. This is illustrated in the third row of Fig. 2.5, which shows the added impact of a transient increase in energy requirement corresponding to neuronal stimulation. Note that these dynamics operate on a very fast time scale (see, e.g., Chap. 6) and are thus not visible on the 10 years scale of the first two rows in Fig. 2.5. The rapid additional energy demand for signalling causes the available ATP levels to drop during the stimulation period, with the drop increasing as the level of a particular risk factor increases (Fig. 2.5a, b). Interestingly, the simulations suggest that steady-state neuronal ATP is particularly robust when the astrocytes contribution is reduced (Fig. 2.5c) but the short-term dynamics reveals a particular vulnerability. In this situation, even though the system maintains its steady state, it is not able to cope with rapid additional perturbations in energy demand and a transient decrease in ATP ensues. From a systems biology viewpoint, this is to be anticipated,

since it is the feedforward function of astrocytes that maintains neuronal ATP during signalling. Taken together, the results of Fig. 2.5 imply that a rigorous investigation of both rapid and long-term dynamics of metabolism in PD is important. This point is covered further in Chap. 7.

Preconditions for PD and Pathogenesis

From the "demand-side", the large energy budgets of vulnerable neurons suggest that energy stress is a precondition for Parkinsonian damage. From the "supply-side", this is reinforced by the observation that the three known PD risk factors are individually associated with a reduced effectiveness of brain energy metabolism, and that their combined impact in creating preconditions would be cumulative. The next question is this: how does the creation of preconditions for PD link to the initiation of the disease state? The pathogenesis of PD is considered in Chap. 7, and as a linkage to that chapter, we now make some bridging remarks between the energy issues discussed here and the cellular mechanisms that are implicated in the pathogenesis of PD.

An insight into the transition between preconditioning and pathogenesis can be gained by considering the two parallel control loops shown in Fig. 2.6a. We consider the class of PD where alpha-synuclein (α-SYN) accumulations are a feature: the upper loop in the figure concerns the energy supply, in which mitochondrial oxidative phosphorylation regenerates ATP from ADP (e.g. the inner feedback loop of Fig. 2.4). The second, lower, loop concerns the positive feedback on reactive oxygen species (ROS), and its implication in the accumulation of mis-folded α-SYN during PD. The full nature of this pathogenic feedback is described in Chap. 7, for the moment it is the linkage between the two feedbacks that is relevant. Specifically, as the energy level at which a neuron operates increases, then the increasing fluxes in the energy supply loop (υ_{op}. υ_{ATP}) drive up the level of oxidative stress, ROS. However, any increase in ROS feeds positively into the level of the protein α-SYN and can stimulate the disease state.

A consequence of the energy/ROS interaction is that the metabolic regimes of oxidative phosphorylation, ATP and ROS overlap. Thus, as shown in Fig. 2.6b in a plot with normalised scales, as ATP flux (υ_{ATP}) increases (corresponding to a larger neuronal energy demand), then so does the flux υ_{op}. The production of ATP can track growing demand (in this synthetic example) for over an order of magnitude change. However, beyond a certain pathogenic point, a rapid growth in ROS is triggered via the ROS feedback. In this "disease" regime, the ROS levels will grow but without an associated energy collapse. How pathogenesis can be triggered in this way is discussed in Chap. 7, the key points suggested by these simulations are the following: (1) a wide level of robustness in ATP supplies exists that can accommodate great variations in energy budgets in different neurons and (2) increasing energy stresses create the preconditions for pathogenesis significantly *before* the energetic capability of the energy metabolism is fully exhausted.

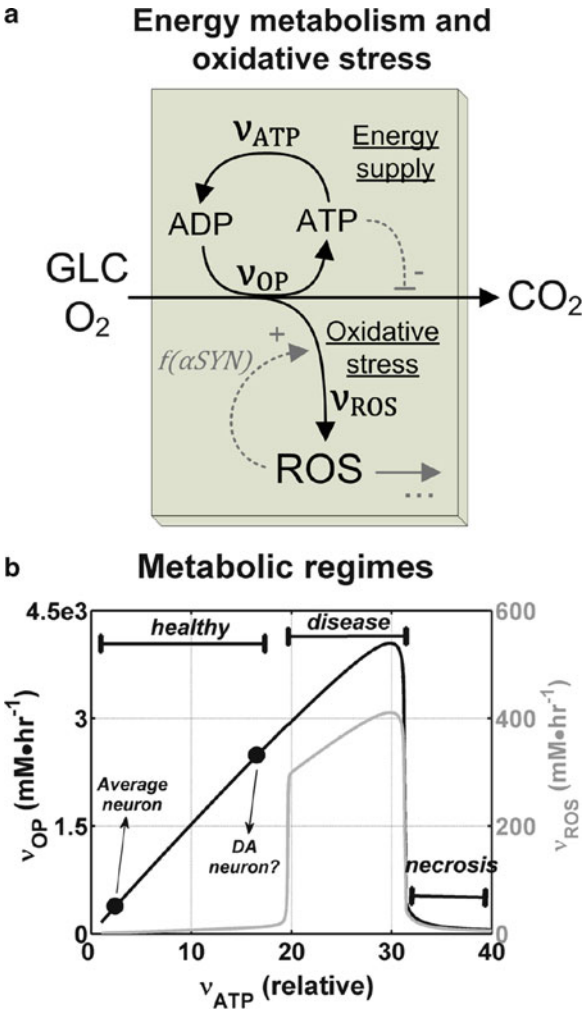

Fig. 2.6 Energy metabolism and oxidative stress. (**a**) Synthetic pathway showing how negative feedback is involved in energy (ATP) regulation and positive feedback is involved in oxidative stress (mediated by α-synuclein as described in Chap. 7). (**b**) Simulations of the system show how energy production (v_{OP}, *black line*) can follow along energy demand (v_{ATP}, *horizontal axis*) for over an order of magnitude, whereas ROS production (v_{ROS}, *grey line*) is initiated at some point before a complete energy collapse occurs. The two points on the energy production line indicate the likely position of the average neuron, and dopaminergic (DA) neurons of the substantia nigra

Discussion

A mathematical model of brain energy metabolism provides a core element in a systems biology approach to neurodegeneration, where multifactorial "wear and tear" is important. In the case of PD, a brain energy metabolism model is particularly relevant since the diversity of risk factors can all be linked to impaired ATP supplies in neurons. Moreover, the brain energy metabolism model provides a quantitative in silico framework for analysing the known risk factors in terms of their impact on brain energy metabolism, and illustrates the proposition that ATP deficits are the common denominator whereby various PD risk factors create the preconditions for pathogenesis. A computer implementation of the model allows

possible mechanisms for risk factors to be simulated over the many years required for them to develop. A structural view of energy metabolism helps to explain the role of rapid signalling in transient ATP deficits. Finally, a consideration of the link between ATP availability and pathogenesis shows how reduced energy levels can feed the process of disease inception (pathogenesis). The descriptions in this chapter are at an overall systems level—further clarity and detail of ageing are given in the following chapter, and relevant cellular mechanisms are explored in other chapters throughout this volume.

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