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PERSPECTIVE ARTICLE

A hypothesis on the equilibrium between dopamine toxicity and detoxification: The roles of NQO2 and UDP-glucuronosyltransferases

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Abstract

NQO2 and tyrosine hydroxylase are co-expressed in dopaminergic neurons. These neurons produce dopamine, a diol, which, under aerobic conditions, can spontaneously revert to the more stable form, the *o*-quinone. *O*-quinones are preferred substrates of NQO2 over *p*-quinones. In *ad hoc* conditions, NQO2 reduces *o*-quinones into the original diols, leading to a futile cycle, the endpoint of which is a strong local production of reactive oxygen species that is deadly for the cells. This futile cycle can be interrupted by the conjugation of dopamine with UDP-glucuronic acid, leading to a glucuronide that cannot be part of the cycle because the glucuronide is not a substrate of NQO2. In this paper, we confer whether this futile cycle could be one of the causes of the specific death of dopaminergic neuronal population that is the signature of some degenerative diseases.

Keywords: Dopamine; Neurodegenerative diseases; Quinone reductase; Glucuronidation; Reactive oxygen species; Toxicity

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1. Drug metabolism and the case of dopamine

Reactive oxygen species (ROS) is a harmful chemical species, and the toxicity of which is well known for decades for its role in a range of pathologies and conditions from cancer[1] to asbestos-induced toxicity[2]. The constant production of ROS and its impact onto subcellular structures (DNA, proteins, and membranes) is associated with the process of aging at the cellular level[3]. More generally, ROS causes harmful lesions in organs in which they are massively generated. To overcome this, a series of antioxidant mechanisms has been developed by evolution[4]. Among other systems, ROS are generated via the redox cycling of quinones, such as menadione[5-7]. We have shown that such a redox cycle occurs in the presence of NQO2, its co-substrate and a series of quinones[8]. We have also shown that the main source of ROS-generating quinone reductase activity in the mouse brain was the activity of the enzyme NQO2[9].

NQO2 is a quinone reductase (E.C. 1.10.5.1) expressed in many tissues of the body[10,11]. Unlike NQO1, NQO2 does not recognize NAD(P)H as a co-substrate, making it a unique example in the literature of quinone reductases[12,13]. Its co-substrates are either

the synthetic *N*-benzyl-dihydronicotinamide (BNAH) or the natural ones: *N*-methyl-dihydronicotinamide (NMH) and *N*-ribosyl-dihydronicotinamide (NRH). The concentration of the latter remains mostly elusive in resting tissues[14-16]. This very fact has led to a key controversy on whether NQO2 is an enzyme with catalytic activity or a pseudo-enzyme without catalytic activity[17], although it remains clear that the same enzyme, NQO2, is present in the genome for several millions of years with the same unique co-substrate recognition as it has been cloned from *Anas platyrhynchos* and *Alligator mississippiensis*[17]. The key questions, which remain unanswered, include: (i) What is its natural co-substrate? Is it NRH? (ii) Where does it come from? Obviously, *in tubo* or *in cellulo*, the enzyme works catalytically and functionally with these co-substrates[11,18,19]. NQO2 reduces *o*- and *p*-quinones when the co-substrate is provided to the pure enzyme[8,13]. NQO2 might have a preferred specificity towards *o*-quinones[20]. This activity also has a "functional" by-product: because the *o*-quinols are particularly unstable, in aerobic conditions, they reversed to their more stable quinone version, while producing ROS[8,20]. Therefore, quinone reductases, by producing diols, indirectly produce ROS species[5,6] in a futile cycle.

Dopamine is an orthoquinol (Figure 1) with a paramount of activities mainly in brain, but also in kidneys and in vasculature[21]. Its dysregulation is involved in degenerative pathologies such as Alzheimer's disease[22] and Parkinson's disease[23], and in general, in neurotoxicity[24]. A link has been suspected for decades between dopamine toxicity and degenerative diseases[25]. Neurons highly expressing this molecule are named dopaminergic neurons, and their death is linked to the progression of these degenerative diseases, at least in some occurrences[26,27]. The definition of dopaminergic neurons corresponds to neurons expressing the tyrosine hydroxylase (TH), an enzyme responsible for the biosynthesis of dopamine from tyrosine[28]. *O*-quinone toxicity has been attributed to the auto-oxidation capacity of its oxidized form[29], although alternative or parallel hypotheses had been explored. The link between dopaminequinone and Parkinson's disease has been reviewed[30-32].

Hydroxylated molecules are eliminated from the body by enzymatic conjugations with polar moieties, such as sulfates or glucuronic acids. These molecules can be endobiotes (bilirubin, steroids, biliary acids, etc.) or xenobiotes (terpenoids, pollutants, and polyaromatic compounds)[33,34]. If not already hydroxylated, they are substrates of the large cytochrome P450 family of enzymes[35]. These enzymes, cytochromes P450 and UDP-glucuronosyltransferases (UGT), are mostly expressed in key organs, that is, liver and kidneys, but also exist in numerous other organs, such as skin and brain[36,37]. UGT, in particular, is clearly active in the brain[38-43]. Incidentally, it has been demonstrated that morphine glucuronide is more active than its aglycone-morphine itself[44,45]. Dopamine glucuronides were identified in mammalian organs and blood[46-51] and found in brain[52-54]. We have also shown that dopamine-treated SH-SY5Y cells expressing UGT1A6 led to the production of dopamine-monoglucuronides, as detected by mass spectrometry[55], demonstrating that dopamine is a substrate of UGT.

We recently showed that NQO2 is co-expressed with tyrosine hydroxylase (TH) in neurons, making this enzyme, by definition, a preferred component of dopaminergic neurons (Boutin and Hirsch, in preparation). We showed

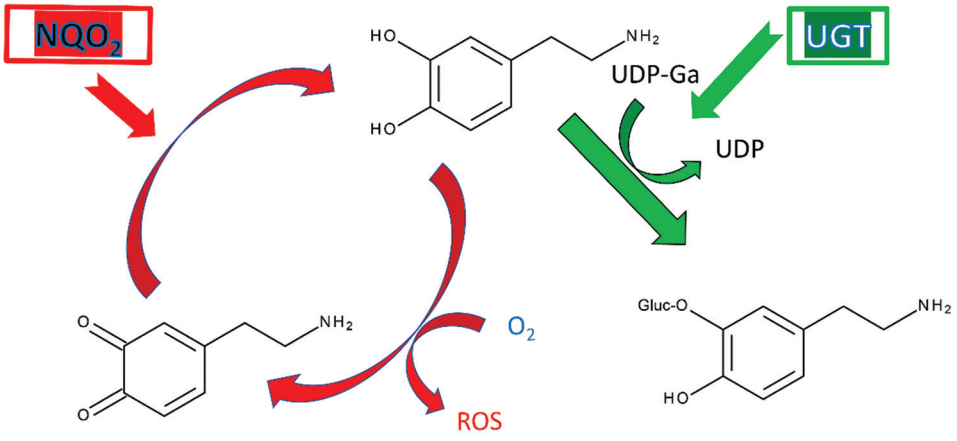

Figure 1. Equilibrium between dopamine toxicity and detoxification. *o*-Quinones can be reduced by NQO2 in the presence of its co-substrate, N-ribosyldihydronicotinamide (NRH), to give an unstable quinol (a diol). This compound, in aerobic conditions, oxidizes back to quinone, generating a burst of toxic ROS. This leads to a futile cycle (quinol/quinone/quinol). *o*-Quinones can be conjugated with glucuronic acid to give glucuronide, thanks to the ubiquitous UDP-glucuronosyltransferase (UGT), in the presence of its co-substrate, UDP-glucuronic acid. Once glucurono-conjugated, the *o*-quinone glucuronide cannot be cycled anymore. The *o*-quinone represented here is dopamine. Red indicates the aspects involved in the toxifying processes, while green the aspects involved in the detoxifying process.

that ROS production in CHO as well as in K562 or SH-SY5Y cells depends on the presence of NQO2. Exploring neurons isolated from NQO2-knockout animals[56], the ROS production was considerably decreased in similar conditions[9]. We concluded that the elevated expression of NQO2 in brain cells in the presence of catechol quinones could lead to ROS-induced cell death via the rapid conversion of superoxide radicals into peroxynitrite by reaction with nitric oxide or into hydrogen peroxide, leading to the highly reactive hydroxyl radicals[9]. Among NQO2 substrates lay oxidized forms of catecholamines such as adrenochrome. Catechols have been shown to co-crystalize with NQO2, which has also been categorized as a catecholamine reductase[57].

In the liver, the activity of oxidoreductase is mainly catalyzed by NQO1, because this enzyme uses NADH as a co-substrate[58,59], which is massively present in liver tissue[60]. NQO2, although expressed in liver, is not capable to reduce compounds due to the low availability of its co-substrate, NRH, as well as the predominant role of NQO1.

Finally, in the last years, the literature reported a possible relationship between NQO2 expression and memory[61-63], before going deeper in a possible relationship between the enzyme regulation and neurogenerative diseases[61,64-67] as well as schizophrenia[68]. These association(s) need further validations, as they were dependent on the patient population tested[69]. Mechanically speaking, an elegant study[70] showed that if the promoter region of *NQO2* gene contains a 29-bp insertion polymorphism, the *NQO2* gene expression is decreased. Mutation in this region would lead to an enhanced expression of NQO2. Such mutation(s) was/were found in post-mortem brain studies of neurodegenerative patients[68]. A physiological hypothesis was also put forward as a possible role for NQO2 in the building of memory[63]. Similarly, we showed that mice devoid of NQO2 were apparently able to learn faster than their wild-type littermates[18,71], linking again memory with NQO2 in a negative correlation way[72]. Reduced NQO2 expression in inhibitory interneurons improves novel object memory. On the contrary, enhanced NQO2 activity would diminish memory after stress episodes[61]. This would form another link between dopaminergic neurons, NQO2 and memory, and following this tentative paradigm, a higher NQO2 expression/activity leads to a lower memory formation[61,73]. On the pharmacological side, potent and specific NQO2 inhibitors, such as S29434 and M11, have neuroprotective properties[18,74].

2. Hypothesis

A speculative but simple idea would be as follows: dopamine is fairly unstable in aerobic conditions, and reacting with oxygen, it is very rapidly transformed in the quinone form. This reaction generates superoxide anions, which decomposes into various ROS (Umek *et al.*[75] and references therein). The kinetic of this reaction is fairly rapid, depending on the pH of the milieu. This reaction occurs concomitantly with the formation of an indole-based quinone for part of the produced oxidized species. The quinone (dopamine quinone or dopaminechrome) is recognized and reduced by NQO2 back into the original quinol in the presence of its co-substrate. Then again, the quinol (dopamine) is oxidized back almost immediately into the quinone. As massive ROS bursts can cause cell death, the colocalization of both dopamine and NQO2 in dopaminergic neurons could be responsible for dopaminergic neuron death, leading to degenerative situations. Thus, the metabolism of dopamine in those neurons is central. Because dopamine glucuronides have been described in brain, and at least one UGT isoform is active in brain, it is clear that if conjugated to glucuronic acid, dopamine cannot enter into this futile cycle of oxidoreduction leading to ROS-mediated toxicity and neuron death.

UGT is a family of conjugated enzymes mainly expressed in liver and kidneys where it detoxifies compounds from the body. UGT is also expressed and active in the brain. NQOs are two enzymes, expressed in many organs. In the liver, the role of NQO1 is clearly to detoxify quinones and to facilitate conjugation, by UGT. Because NQO1 recognizes NADH, which is massively present in the liver, its role is preponderant in this organ, while in the brain, the possible role of NQO2 is speculated in this context. NQO2 does not recognize NAD(P)H as a co-substrate. The origin of NRH remains poorly explored. On the neuron side, the absence of conjugation leads to a futile cycle between quinone and quinol that produces ROS, a toxic entity to the cells.

In summary, as shown in Figure 2, in liver, the predominance of NQO1 and its co-substrate NADH as well as the large amount of UGT and UDPGa, its co-substrate, makes the metabolism of quinone quite safe, from reduction to diol followed by conjugation. In brain, though, the co-expression of NQO2 and tyrosine hydroxylase (TH) might render the installment of this futile cycle very rapid, depending on NQO2 co-substrate availability. The possible role of UGT in this organ is less clear, but the conjugation of diol might stop the quinol/quinone futile cycle. Nevertheless, the presence of dopamine-glucuronides in cerebrospinal fluid[53] indicates the presence of at least one UGT isoform in the brain.

An equilibrium between the conjugation of dopamine and its entrance in the quinone/quinol futile cycle would drive the overall possible toxicity of dopamine, under

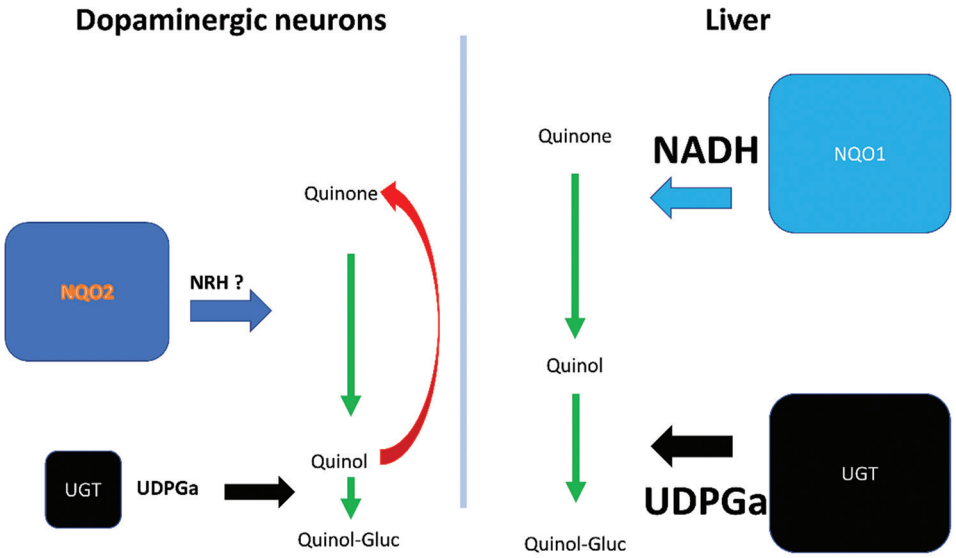

Figure 2. Quantitative comparison in the dopamine toxicity and detoxification equilibrium between liver and brain.

those particular circumstances. Furthermore, a glimpse into the quantitative (very low) and timely (over long period of times) activity of NQO2 would be in line with a low accumulation of ROS in dopaminergic neurons. Therefore, it would translate into the slow injuries and ultimately death of those neurons corresponding to the evolution (worsening) of the degenerative situation over the course of Parkinson's disease[76,77] as well as of Alzheimer's disease[78,79], for example. Among the counteracting mechanisms, UGT could stop or at least limit the cycle, and thus lower the production of ROS. We showed that, in the presence of UGT and UDP-glucuronic acid, the amount of ROS generated during an incubation of cells expressing both UGT and NQO2 in the presence of NRH was strongly diminished[55]. We also showed that in cells, and in the presence of its co-substrate, the main source of ROS production is NQO2, because cells derived from brain of NQO2-knockout mice studied under identical conditions produced marginal amount of ROS[9]. It should be mentioned that the dichotomic role of dopamine in neurodegenerative diseases can be protective and hazardous to them[26,80,81].

Another aspect of the regulation of UGT might be taken into account. It is known for decade that phenobarbital is an inducer of at least some UGT isoforms. These were one of the first pre-cloning proofs of the multi-isoform nature of UGT[82]. The use of differential inductions (phenobarbital and 3-methylcholanthrene) clearly showed the paths towards later characterizations of the UGT isoforms, their purifications and finally, their clonings[33,83]. Furthermore, the use of phenobarbital to try to compensate Crigler-Najjar syndrome or the newborn jaundice has been reported[84,85], showing that the induction of UGT actually works in human. It would be important to verify if such induction of UGT changes (delays) the development of degenerative diseases.

Other conjugative systems present in the brain, such as the sulfotransferases, might also lead to a similar situation[86,87], provided that sulfo-conjugated quinols cannot be substrate of NQO2 (in order to stop the cycle), which probably is the case.

In brief, the amount of available UGT co-substrate, UDP-glucuronic acid, is enough to permit the elimination of dopamine as glucuronide, and most importantly, to identify and quantify the amount of NQO2 co-substrate essential to its activity. Among the possible co-substrates are either NRH, sometimes described as resulting from NADH catabolism, or various nicotinamide catabolites[15,16]. What would make the most sense would be that, under lethal stress, NADH breakdown occurs because cells are in search of adenosine source. When adenosine monophosphate (AMP) molecules are exhausted, NADH would be the next reservoir of nicotinamide derivatives, because its cleavage results in a molecule of AMP and one of nicotinamide.

The respective regulations of NQO2 and UGT expressions are known to depend on environmental factors, such as various pollutants[88-90], that would lead to their differential expressions during life, possibly making the changes in the expression of these enzymes, or the availabilities of either co-substrates, a regulator of the NQO2-dependent neuron toxicity.

As pointed out earlier, the association of some neurodegenerative diseases and enhanced NQO2

Box 1. State of the art and future trends

(A) What is known

(i) Dopaminequinone is spontaneously generated in brain from dopamine.

(ii) Dopaminequinone is a substrate of NQO2 in the brain.

(iii) NQO2 and TH are co-expressed in the dopaminergic neurons.

(iv) NQO2 catalytic activity indirectly leads to the production of ROS.

(v) UGT1A6 produces glucuronide of dopamine.

(vi) UGT is expressed in the brain and glucuronides are found in the LCR.

(vii) UGT can be induced by phenobarbital in human.

(viii) Glucuronidation of dopamine interrupts the futile cycle catalyzed by NQO2, resulting in the cessation of ROS production.

(B) What remains to be demonstrated or reinforced

(i) The presence of UGT in the brain, and its subcellular localization, including at the levels of the neurons as well as its possible co-expression with NQO2.

(ii) The nature of the UGT isoform should be clarified (UGT1A6 or UGT1A10) in the brain.

(iii) The availability of the NQO2 co-substrate (e.g., NRH or NMH).

(iv) The constant but low activity of NQO2 in dopaminergic neurons. (This would correspond to a continuous production of ROS at low levels, and it could correspond to a long process of minimal but repetitive accumulation of injuries in dopaminergic neurons).

(v) The regulations of both NQO2 and UGT expressions – at least the particular isoform in charge of dopamine conjugation. (Particularly regarding their modulations by pollutant factors, in order to document the possible antagonistic effects of UGT dopamine conjugation onto NQO2-dependent toxicity).

(vi) At the cohort levels, could phenobarbital (as inducer of UGT) delays the onset of neurodegenerative diseases?

(vii) Alternative conjugation pathways might play a similar limiting role, such as sulfotransferase(s). (Further studies should complete the picture, in particular, the availability of the co-substrate in the brain, and expression level variation throughout life).

expression is an indication that in some of those pathological situations, NQO2 might have a causal role. Nevertheless, it is highly improbable that every type of neurodegenerative situations is due to both NQO2 and UGT dysregulations. The present commentary is based on our thinking about the enzymes and the situations we encountered over the last 4 decades. To further explore this hypothesis, Box 1 lists the simple questions to be answered in this area. Since they do not seem to be in the mainstreams of neurodegenerative disease research, they may be understudied. Of course, more experiments are warranted to test this hypothesis.

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Conflict of interest

The authors declare no conflict of interest.

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Ethics approval and consent to participate

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Consent for publication

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Availability of data

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