Pharmaceutical Regulatory Affairs: Open Access

Karachitos, et al., Pharmaceut Reg Affairs 2015, 4:4
DOI: 10.4172/2167-7689.1000157

Review Article Open Access

VDAC as a Potential Target in Huntingtons Disease Therapy: The State of the Art

Andonis Karachitos, Daria Grobys and Hanna Kmita*

Laboratory of Bioenergetics, Institute of Molecular Biology and Biotechnology, Adam Mickiewicz University in Poznań, Umultowska 89, 61-614 Poznań, Poland

***Corresponding author:** Hanna Kmita, Laboratory of Bioenergetics, Institute of Molecular Biology and Biotechnology, Faculty of Biology, Adam Mickiewicz University, Umultowska 89, 61-614 Poznań, Poland, Tel: +4861 829-5901; E-mail: kmita@amu.edu.pl

Rec date: Nov 24, 2015; **Acc date:** Dec 24, 2015; **Pub date:** Dec 28, 2015

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Abstract

It is becoming increasingly evident that mitochondria dysfunction plays an important role in pathogenesis of Huntington's disease (HD). However, the underlying mechanism is still needs to be explained. The crucial aspect of the explanation is to indicate the upstream events in mitochondria dysfunction that could contribute to HD. In the review we propose the defect of voltage-dependent anion-selective channel (VDAC), as a causative event in HD-related mitochondria dysfunction. Thus, we propose to consider VDAC as a crucial element in HD etiology and consequently as a reasonable target for therapeutic interventions in HD, based on developing novel therapeutic strategies eliminating mitochondria dysfunction.

Keywords: Huntington's disease; VDAC; Mitochondria; Therapy

Huntington's Disease

Huntington's disease (HD) is a progressive and fatal neurodegenerative disease with a prevalence of about 5-10/100 000. Clinically, the disease is characterized by progressive chorea (involuntary dance-like movements), rigidity, weight loss, dementia, seizures and psychiatric disturbances such as depression, withdrawal and irritability. These symptoms including cognitive deterioration, psychiatric disturbances, and movement disorders result from a selective and continuous loss of neurons from the striatum and deep layers of the cerebral cortex although other brain regions such as thalamus and subthalamic nucleus are also affected [1-3]. Current treatments for HD relieve merely the symptoms and address the control of behavioral symptoms, motor sedatives, cognitive enhancers, and neuroprotective agents [4,5] but are not able to restore neuronal function nor to stop the insidious loss of neurons. As summarized by Kumar et al. [6], although there is an intensive research concerning development of neuroprotective strategies such as fetal neural transplantation, RNA interference (RNAi) and transglutaminase inhibitors (TGaseI), effective therapeutic strategies may not be developed until the next few decades. Thus, a new therapeutic approach involving new potential targets and to start before the symptomatic stage could contribute to HD treatment to be more specific and effective. This, in turn, requires further studies concerning molecular mechanisms underlying HD.

The genetic hallmark of HD is an expansion of an unstable trinucleotide CAG repeat region within the first exon of the gene encoding the protein Huntington (Htt). This results in synthesis of its mutant form (mHtt) containing more than 36 glutamine residues at N terminus although the possible contribution of mHtt encoding mRNA, i.e. toxic mRNA in HD etiology has also been suggested [7]. HD inheritance is autosomal dominant and consequently the prevailing view is that mHtt mediated symptoms result from a toxic gain-of-function mechanism although loss-of-function mechanisms for mHtt and Htt are also proposed [8,9]. Htt is conserved among vertebrates [10], is localized mainly in cytoplasm and exhibits anti-apopptotic properties [11,12]. Importantly, Htt expression in different tissues does not correspond with the restricted distribution of neuropathologic changes in HD [13] but the protein has been shown to be required for mammalian neurogenesis [14]. Its domain model does not indicate any particular functions aside from domains that might mediate protein interactions. Indeed, numerous reports indicate that Htt interacts with above 200 proteins which represent a diverse array of biological functions, including synaptic transmission, cytoskeletal organization, signal transduction, gene expression regulation and metabolism [8,15-17].

Presently available data indicate at the following mechanisms of mHtt toxicity: protein aggregation, excitotoxicity, oxidative stress, impairment of proteolysis and proteasome, enhanced apoptosis and autophagy, transcription regulation, including epigenetic mechanisms and mitochondria dysfunction [6,8,9,18-20]. Although the functional relationship of Htt to mitochondria is still uncertain [21], it is becoming increasingly apparent that mHtt can impair mitochondrial function directly [22]. Moreover, available data indicate that mitochondrial defects may initiate the disease onset [23-31]. Accordingly, the current PubMed searching for "Huntington disease and mitochondria AND review" indicate over 130 review papers addressing mHtt effects on mitochondrial bioenergetics and biogenesis, protein import, complex assembly, fission and fusion, mitochondrial transport including Ca^{2+} and metal homeostasis, and on the degradation of damaged mitochondria via autophagy (mitophagy). Simultaneously, it is also evident that VDAC (voltage-dependent anion-selective channel), regarded as a dynamic regulator, or even governor, of mitochondrial functions, contributes to affected phenomena directly or by interacting with the involved proteins. The fields of possible interference between the processes impaired within the postulated mechanisms of HD pathogenesis and VDAC-affected processes are shown in Figure 1.

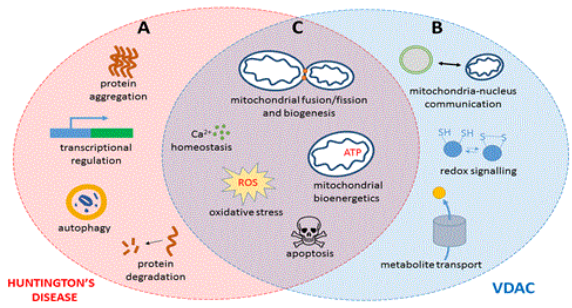

Figure 1: Premises for VDAC involvement in HD pathogenesis. Schematic representation of the cellular processes affected in Huntington's disease (A) and affected directly or indirectly by VDAC (B). The overlapping area (C) indicates possible upstream events in mitochondria dysfunction detected in HD that could result from impaired VDAC functions.

VDAC as a versatile protein

The main function of VDAC is metabolite exchange between mitochondria and cytoplasm. Importantly, VDAC gating is currently regarded as the major mechanism of the mitochondrial outer membrane permeability control [32]. Accordingly, as shown in Figure 2, the channel participates in superoxide anion release from mitochondria, ATP rationing, Ca^{2+} homeostasis, and apoptosis execution [33-36]. Moreover, using Saccharomyces cerevisiae as a model system it has been demonstrated that VDAC mediates the intracellular reduction/oxidation (redox) states and in this way contributes to expression level regulation of different proteins and to communication between mitochondria and the nucleus [37-39]. Thus, VDAC is regarded as a protein decisive for cell life and death [36,40]. Accordingly, the available data suggest that VDAC malfunction may be crucial for Alzheimer disease [41-43], Down's syndrome [44], epilepsy [45,46] and familial amyotrophic lateral sclerosis [47,48] as well as to cancer [49].

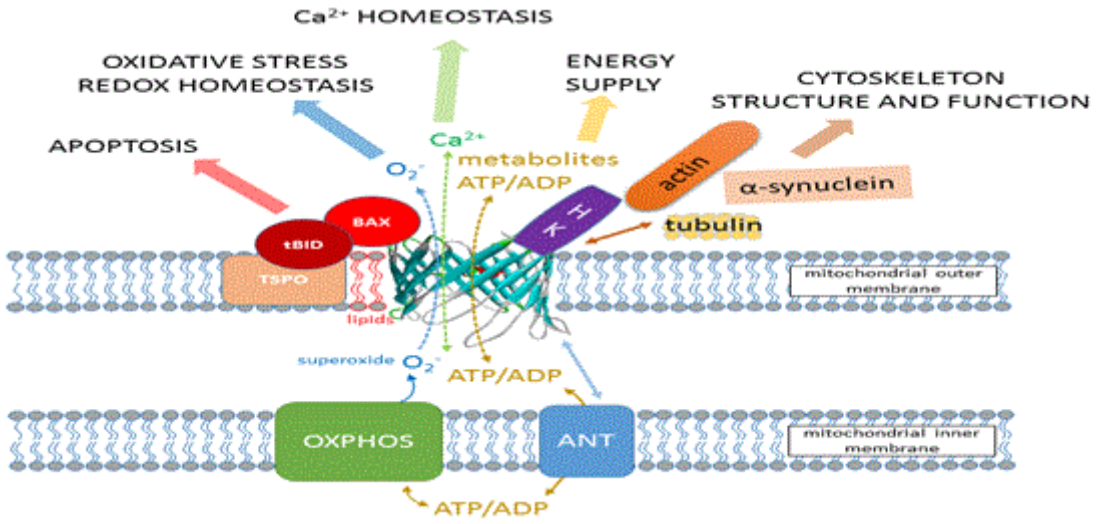

Figure 2: Direct interactions of VDAC with cellular proteins and lipids and their contribution to cell functioning. HK-Hexokinase; OXPHOS–Proteins involved in the Oxidative Phosphorylation (the respiratory chain and ATP synthase); TSPO–Translocator Protein (18 kDa).

Interestingly, in mitochondria of different organisms VDAC may be present as isoforms encoded by separated genes, displaying different channel-forming activities and playing different roles in cell metabolism and survival [36,40,50,51]. For example, in human mitochondria, as in the case of other vertebrates, three isoforms of VDAC (VDAC1-VDAC3) able to form functional channels have been identified. They are expressed in different tissues and organs at different levels. Translating characteristics of the VDAC isoforms into in vivo functions is still a challenge that may be resolved by application of animal models of VDAC isoform deficiency providing information concerning the isoform-specific functions in cell functioning [52].

Some of these functions depend on their interaction with other proteins in the cytosol and the mitochondrial intermembrane space and are affected by VDAC posttranslational modification, mainly phosphorylation [53]. It has been recently shown for rat VDAC1 that nitrosation not only decreases its conductance but also significantly enhances its appearance in a closed state whereas phosphorylation protects the channel against closing [54]. However, VDAC sensitivity to oxidative modification should not be neglected [e.g., 55]. Accordingly, it has been shown that in the presence of oxidative modification/damage of VDAC the control of the mitochondrial outer membrane permeability might be severely affected leading to mitochondria dysfunction [56-59]. Moreover, the available data suggest that VDAC isoforms may be differently controlled by oxidative modification of cysteine residues. For example it has been shown for human VDAC3 that the cysteine residue modification might be crucial for its channel activity under physiological conditions [60].

The channel properties of VDAC were first reported in 1976 [61] and since that time have been extensively studied [33,36,62]. In a brief, VDAC reconstituted into artificial membranes displays only one fully

open state, which is anion-selective. At higher potentials VDAC exhibits lower conductance and cation-selective states called closed states. However, the channel behavior of reconstituted VDAC is not the same as that of native one located in the mitochondrial outer membrane as several endogenous factors were indicated to modulate VDAC activity, including NADH [63], Ca^{2+} [36], tubulin [64,65], tBid [66] and other members of Bcl-2 protein family [67], hexokinase I and II [36], α-synuclein [68], 18 kDa Translocator protein (TSPO) [69,70] as well as mitochondrial lipids [71] and still unidentified cytoplasmic and mitochondrial proteins [72]. As summarized by [73], VDAC interactions with different proteins contribute to apoptosis, cytoskeleton functions, Ca^{2+} and oxidative-redox homeostasis as well as energy transformation (Figure 2). There are also data pointing at interaction between VDAC and mitochondrial trafficking and fusion/fission machinery [74,75]. Consequently, VDAC modulation may affect processes that are known to be affected by VDAC directly; i.e., the respiratory chain, transcriptional regulation and protein import, Ca^{2+} balance, oxidative stress and apoptosis, or might be affected due to interaction between VDAC and the involved proteins. Thus, conductance of VDAC in living cell needs to be studied in details in order to better understand VDAC function in vivo and effect of VDAC modulators in therapy, including the isoform specificity. However, as mentioned by [76], it is still not clear whether VDAC is intrinsically open in living cells as suggested by the low permeability barrier of the mitochondrial outer membrane or is closed. Therefore, answering the question appears to be important for development of new therapeutic interventions based on VDAC modulators.

VDAC as a therapeutic target

Consistently with the crucial role of VDAC in mitochondrial functioning, VDAC can be regarded as a candidate for effective pharmacological treatment. Taking into account the available data concerning VDAC role in cell life and death [36], the treatment could be based on cytoprotective or cytotoxic strategies. Undoubtedly, impairment of the cell death pathways resulting in their excessive or insufficient activity plays a crucial role in the pathophysiology of several diseases, including cancer, muscular and myocardial diseases as well as neurodegenerative diseases [36,73,77]. However, as mentioned by [73], a given drug interaction with purified VDAC resulting in modulation of its channel activity do not necessarily indicate that this interaction will result in cytotoxicity or cytoprotection. On the other hand, as shown in Table 1, the list of VDAC modulating compounds and affecting cell survival that have been already registered or are during preclinical or clinical trials is not very long.

Modulator	Mechanism	VDAC Conductance	Cell death	Therapeutic potential	Clinical status	References
DMA III	direct interaction	ND	Induction	Chemotherapy to induce apoptosis	Preclinical	[91]
FNQs	VDAC-dependent ROS production	ND	Induction	Chemotherapy to induce apoptosis	Preclinical	[101]
Oblimersen (G3139)	direct interaction	Block	Induction	Chemotherapy to induce apoptosis	trade name Genasense; over 45 clinical trials including lymphoma and melanoma; still not in clinical practice	[89]
Methyl jasmonate	Inhibit HK-VDAC interaction	ND	Induction	Chemotherapy to induce apoptosis	Preclinical; only case report: promising for precancerous and cancerous skin lesions	[90]
Cisplatin	direct interaction; human VDAC1 upregulation	ND	Induction	Chemotherapy to induce apoptosis	trade name Cisplatin; chemotherapy and anti-cancer drug: metastasis of tumors located in ovary, testis, bladder as well as head and neck area; still at clinical trials (overall 1928)	[73]
Erastin	Inhibit VDAC oligomerization; reduce VDAC permeability to NADH	ND	Induction	Chemotherapy to induce apoptosis	Preclinical	[80]
DIDS	direct interaction, Inhibit superoxide release from mitochondria	Decrease	Inhibition	ND	Preclinical	[73]
Minocycline	direct interaction	Decrease/ Modulate	Inhibition	Cytoprotection, including neuroprotective and	Case reports: promising for schizophrenia, psychotic symptoms and bipolar depression** – accordingly, e.g. bipolar disorder depression: 3 trials, phase III and IV; schizophrenia: 6 clinical trials including phase III and IV.	[109-112]

				immune-modulating properties	Clinical trials indicate the lack of therapeutic capability in ALS and Huntington disease although indicate the capability in Parkinson disease (phase II). At present clinical trials concerning e.g. Alzheimer disease (phase II), stroke (from phase I to phase IV) and fragile X Syndrome	
Rasagiline	direct interaction	Decrease/ delayed opening	Inhibition	Cytoprotection	trade name Azilect; applied in Parkinson's disease; overall 44 clinical trials; also investigated for the treatment of Alzheimer's disease	[97]

Table 1: VDAC modulators and their therapeutic potential. Based on ww.w.ClinicalTrials.gov.; http://clinicaltrialsfeeds.org/clinical-trials. Abbreviations: DMA III-Dimethylarsinous Acid; 4,4'-Diisothiocyanostilbene-2,2'-Disulfonic Acid; FNQs-Furanonaphthoquinones.

The list contains mainly cell death-inducing drugs suitable for anti-cancer therapy. They include "mitocans" and proapoptotic factors. The term "mitocans" reflects the drug mitochondrial targeting and anti-cancer effect. Importantly, one of the postulated targets for the drugs is VDAC [78,79] and the activity has been shown for furanonaphthoquinones (FNQs), erastin and cisplatin although it should be emphasized that the drugs target different isoforms of VDAC [80-84]. Moreover, only cisplatin is used in clinical practice as anti-cancer drug. The proapoptotic compound of potential anti-cancer activity, i.e. oblimersen (phosphorothioate antisense oligonucleotide targeted to the initiation codon region of the Bcl-2 mRNA, known also as (G3139), dimethylarsinous acid (DMA III) and methyl jasmonate are known to interact with VDAC as well although in the case of the latter the interference with VDAC-other protein interaction has been shown [85-94].

The list contains also drugs with cytoprotective activity represented by DIDS (4,4'-diisothiocyanostilbene-2,2'-disulfonic acid), minocycline, rasagiline and fluoxetine (Prozac). The therapeutic potential of DIDS has not been defined yet but the rest of the drugs are regarded as potential neuroprotective ones [77,95]. Interestingly, fluoxetine is a potent antidepressant drug, rasagiline (N-propargyl-1-(R)-aminoindan) is an anti-Parkinson drug, also described as drug effective in treatment of Alzheimer disease [96,97] whereas minocycline (7-dimethylamino-6-dimethyl-6-deoxytetracycline) is an antibiotic of the tetracycline family that has multi-faced effects on cell functions and consequently a number of clinical properties including cytoprotective and neuroprotective potency [98,99]. However, a long-term, double-blind, placebo-controlled trial appears highly warranted for definitively establishing the value of minocycline in HD [100].

It should be also mentioned that important part of anti-cancer and neuroprotection strategy including VDAC is silencing or enhancement of the channel expression. For example, it has been shown that overexpression of VDAC1 increases the anti-cancer activity of FNQs, endostatin, cisplatin, mechlorethamine and melphalan [101-103]. Overexpression of VDAC1 has been also reported to shift its equilibrium status towards the oligomer state that is proposed to be crucial for the release of pro-apoptotic proteins from mitochondria resulting in cell death [101,102]. Accordingly, the presence of different cell death modes with overlapping characteristics [104,105] suggests possible VDAC-targeted anti-cancer therapies based on modulation of cell death modes other than apoptosis but the area is still unexplored. On the other hand, interesting approach in VDAC-mediated anti-cancer therapy has emerged due to observation that interaction of viral proteins with VDAC isoforms can trigger cell death [106]. Neuroprotective strategy may also consist in regulation of VDAC expression. It has been demonstrated that the known neuroprotective activity of asiatic acid (a triterpenoid) may result from its free radical scavenging activity as well as from regulation of VDAC expression at the level of transcription and translation [107]. Moreover, VDAC is also included in development of microRNA-based therapeutics for several neurodegenerative disorders [108].

Potential role of VDAC in HD

As mentioned above, it is becoming increasingly apparent that mHtt can impair mitochondrial function directly by affecting mitochondrial bioenergetics and dynamics [31]. Undoubtedly, neurons are highly dependent on mitochondria ATP production and Ca^{2+} buffering to maintain excitability, gene expression and synaptic communication, and rely on dynamic trafficking of mitochondria to adapt this limited resource to the variable needs of distant processes in vast neuritic networks. Moreover, neurons require efficient biogenesis and mitophagy to renew or adapt mitochondria levels throughout their lifespan, and proper fusion and fission to allow mitochondria functional and spatial segregation. Thus, distinct mitochondrial roles in neuronal physiology might be affected in HD etiology. Importantly, the affected mitochondria functions include processes that are known to be influenced by VDAC. It has been shown that VDAC contributes to the processes directly or indirectly by interacting with the involved proteins. On the other hand, VDAC may promote cytoprotection including neuroprotection [77,109]. Thus, VDAC may play a central role in mitochondria dysfunction detected in HD (Figure 1) and its attenuation and consequently in HD treatment. However, searching of PubMed provides only two review papers pointing at putative contribution of VDAC to neurodegeneration, including HD [27,46] and one experimental paper concerning the role of VDAC expression regulation in neuronal cell survival in the brain and the significance of the mechanism to neurodegenerative disease including HD [108]. Accordingly, our preliminary results suggest interaction of human VDAC isoforms with both Htt and mHtt (unpublished results).

The issue implicate answering to the following three basic questions: (1) does the presence of mHtt result in changes of VDAC channel activity?; (2) do the changes in VDAC activity result from direct interaction of mHtt with VDAC or from the channel modification caused in the presence of mHtt or from the elimination of Htt effect?; and (3) do the changes in VDAC activity trigger mitochondria dysfunction postulated for HD pathogenesis? Explaining whether VDAC defect is a causative event in HD pathogenesis and whether VDAC impairment is caused by its direct or indirect interaction with mHtt, could possibly narrow down the drug targets to be more specific and effective in blocking or controlling cell death by enabling the recovery of mitochondrial function and structure. Thus, resolving the role of VDAC in HD pathogenesis may be important for development

of new therapeutic strategies concerning the disease as well as other neurodegenerative diseases.

Acknowledgement

The work was supported by grant from the National Science Centre (Poland), namely NCN - 2011/01/B/NZ3/00359 and the "KNOW RNA Research Centre in Poznań" (grant no. 01/KNOW2/2014).

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