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Targeting the mitochondrial electron transport chain in autism, a systematic review and synthesis of a novel therapeutic approach

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Running title: electron transport chain in autism

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Abstract

Autism is a complex developmental disorder with an unknown etiology and without any curative treatment. The mitochondrial electron transfer chains play a major role in the production of ATP, and the generation and management of reactive oxidative stress (ROS). This paper is a systematic review of the role of the mitochondrial electron transport chain in autism, and a consequent hypothesis for treating autism is synthesized.

An electronic search with pre-specified inclusion criteria was conducted in order to retrieve all the published articles about the mitochondrial electron transport chain in autism. The two databases of PUBMED and Google Scholar were searched.

From one hundred twenty five retrieved titles, 12 (three case control study and 9 case reports) articles met inclusion criteria. All of the included studies indicated dysfunction of electron transport chain in autism.

The mitochondrial electron transfer chain seems impaired in some children with autism and ROS production is additionally enhanced. It is hypothesized that interventions involving alternative electron shuttling may improve autism through lowering the production of ROS. In addition, it is expected that this alternative electron shuttling to cytochrome c might enhance the production of ATP which is impaired in the disorder.

Keywords: mitochondria, autism, treatment, energy, oxidative stress, aetiology.

Introduction

Electron transport chain

Three quarters of a century ago, it was first hypothesis that neuropsychiatric disorders might involve abnormalities in energy generation (Looney and Childs, 1934).More than half of a century ago, it's been known that energy is normatively produced thorough the oxidative phosphorylation process, whereby electrons are shuttled across a series of specific carriers (Boveris et al., 2000; Chance and Williams, 1955, 1956; Turrens, 1997, 2003). These carriers, the mitochondrial enzyme complexes named complex I, complex II, complex III, and complex IV, are located in the inner membrane of mitochondria. Electrons enter this chain through complex I and complex II, and cascade onto the other complexes. Finally, an electron is transferred to O2 to produce H2O (Chance and Williams, 1956; Mimaki et al., 2011). These stepwise transfers lead to the serial pumping of protons into the mitochondrial inter-membrane space. These protons are used for ATP production by ATP synthase (complex V) (Mimaki et al., 2011).

Electron transferring chain and Reactive oxygen species generation

Reactive oxygen species (ROS) are mainly produced in mitochondria. But it is not clear exactly how ROS are produced as a result of electron transfer in the electron transfer chain (Selivanov et al., 2011). ROS production is enhanced in pathological conditions such as mitochondrial electron transport impairment (Sugioka et al., 1988). Backward electron transfer, in which electron is transferred from succinate to complex I and NAD+ can also generate ROS (Schonfeld and Wojtczak, 2007).

All the mitochondrial enzyme complexes can generate ROS (Jastroch et al., 2010). The main source of superoxide production by respiratory chain is from the redox component of Complex I and III (Skulachev, 2007; Vinogradov and Grivennikova, 2005). However, Complex III has a principal role (Chen et al., 2003). In fact, deficiency of mitochondrial complex I which is the first complex of the oxidative phosphorylation system is associated with reactive oxidative stress production (Blanchet et al., 2011). Moreover, the production of H_2O_2 is enhanced after the blockade of complex I. It oxidizes NADH which is the substrate of complex I. During oxidation of complex I substrates, complex III generates ROS (Chen et al., 2003). This production of ROS can be prevented by rotenone (Chen et al., 2003). The inhibition of electron transfer to cytochrome oxidase increases the production of ROS mainly from complex I (Chen et al., 2003). This role of complex I in the generation of ROS had been previously reported (Grivennikova and Vinogradov, 2006). Accordingly, more than 50% of total ROS generation in brain homogenates is attributable to complex I (Kudin et al., 2008). Besides, Complex I inhibition also causes depletion of ATP, impairing all ATP dependent cellular activities (Gandhi and Wood, 2005). Complex I deficiency and increased oxidative stress is noted in other neuropsychiatric disorders such as bipolar disorder (Andreazza et al., 2010), and interacts with synaptosomal-associated protein 25 (SNAP-25), a protein that plays a role in membrane fusion, synaptic vesicles and plasma membranes.

The complex III site also contributes to superoxide production when energy load is high (Malinska et al., 2010). The main origin of ROS generation, when complex I is oxidized, is complex III (Chen et al., 2003). This complex may be targeted to decrease ROS production. For example, a complex dietary supplement containing ingredients such as vitamins B, E,

C, D, Magnesisum, Manganae, and L-Glutathione increase complex III in old age it decreases the generation of free radicals in mice (Aksenov et al., 2011).

Autism

There are many reports about the association of reactive oxygen species (ROS) and autism (Rossignol and Frye, 2011), and the possible role of oxidative stress in the neurobiology of autism is emphasized by contemporary reviews (Ghanizadeh et al., 2012; Villagonzalo et al., 2010). There is a higher incidence of mitochondrial dysfunction in autism than the controls (Haas, 2010). These data will be discussed in succeeding sections.

ATP production and plasma level of lactate

The activities of Na(+)/K(+)ATPase and creatine kinase (CK) in autism are significantly higher than that of controls (Al-Mosalem et al., 2009), however, the activity of adenosine diphosphatase (ADPase), which has an important role in generation of energy, was not statistically higher than that of the controls. In addition, the plasma lactate level was higher (Al-Mosalem et al., 2009). Lactate production is enhanced when glycolysis is promoted not only when Complex V or IV are inhibited (Wen et al., 2011). Plasma levels of lactate in autism are higher than that of controls (Chugani et al., 1999). Curiously,

elevations in lactate in neuropsychiatric disorders is one of the first biomarkers ever detected(Looney and Childs, 1934).

Electron transferring chain and autism

Mitochondrial disorders are frequently reported in autism (Haas, 2010), and impairment of the mitochondrial respiratory chain has been noted in 7.2% of children with autism (Oliveira et al., 2005). This rate in the general population was about 0.01%. An electronic systematic review was conducted. is the aim of this paper was to collect data about the association of electron transport chain with autism and raise hypotheses about mitochondria as a possible therapeutic target for treating autism in children and adolescents.

Methods

Search strategy

A search protocol was developed for this systematic review in order to retrieve all the published articles regarding the mitochondrial electron transport chain in autism. The databases PUBMED and Google Scholar were electronically searched. No publication time was considered as an inclusion criterion. The search to find the publications was conducted on March 2012, updated on September 2012. The search terms were: 'autism', 'autistic', 'ASD', 'pervasive', and 'pervasive developmental disorder' in all combinations with the terms 'electron transport chain', 'mitochondrial respiratory chain' and 'electron'.

Study selection

The titles and abstracts of the retrieved publications were reviewed. Published articles from peer-reviewed journals included patients with autism spectrum disorders and reported findings about electron transport chain were included. The flow chart of articles is displayed in Figure 1. Exclusion criteria were: studies did not report experimental findings from human or animals, no new data are reported, and lack of any report about the electron transport chain in autism. Overall, twelve publications presented unique data that met the current inclusion criteria.

Data extraction and validity assessment

The references of the included retrieved articles were further examined to find other possible publications. The abstracts were reviewed. The extracted data and characteristic of studies are displayed in Tables 1 and 2.

Results

From one hundred twenty five retrieved titles, 58 were duplicated. The title and abstract of 54 articles were irrelevant. Twelve articles met inclusion criteria. All of them were in English and none of them reported findings from studies included animal subjects (Figure 1).

Study characteristics

Case control studies

A study showed that 6 out of 10 children with autism had low level of complex I (Giulivi et al., 2010). Another study investigated the levels of mitochondrial electron

transport chain (ETC) complexes I, II, III, IV, and V, in brain tissue of individuals with autism. They indicated that there was lower levels of complexes III and V in the cerebellum, of complex I in the frontal cortex, and of complexes II, III, and V in the temporal cortex of children aged 4 to 10 years with autism when compared to that of age-matched control children (Chauhan et al., 2011). However, these difference were not found in adults with autism (Chauhan et al., 2011).

Case reports

A case report of a 3 year old girl showed that a partial deficiency of complexes III and IV of the respiratory chain in autism (Guevara-Campos et al., 2010). Another case report of a 12 year old boy with mental retardation, autism, epilepsy, and leg weakness showed that the level of complex IV was severely decreased and complex I activity level was mildly decreased in a buccal swab sample (Ezugha et al., 2010). Another report, including two autistic children with a chromosome 15q11-q13 inverted duplication, showed a partial respiratory chain block, which was most prominent at the level of complex III (Filipek et al., 2003). Moreover, the enzymatic activities for complex I and III were decreased in a girl with autism (Poling et al., 2006). In addition, the activity level of complex IV was near 5% of the control values (Poling et al., 2006). Complex I is the most commonly reported abnormality in autism, with reported deficiency of up to 64%. The percentages for complex II, III, and IV are 8%, 20%, and 4%, respectively (Weissman et al., 2008). The latter study included 25 patients with ASD.

Discussion and synthesis of a hypothesis for treating autism

As noted above, there are reports of an association between alterations in the mitochondrial electron transport chain and autism (Frye et al 2012; Haas 2010:). However, the paucity of data suggests that electron transport chain changes in autism are not a well-researched area, with most of the publications representing case reports. There are only three case control studies (Chauhan et al., 2011; Giulivi et al., 2010; Taurines et al., 2010). Two of these studies suggested electron transport chain impairment in autism (Chauhan et al., 2011; Giulivi et al., 2010). The other case control study included a group of children with autism and a group of children with schizophrenia (Taurines et al., 2010). They reported that the expression analyses of the mitochondrial complex I 75-kDa subunit in autism was in the normal range (Taurines et al., 2010). They did not investigate the different elements of the electron transport chain. In addition, all of the case reports supported the possible association of electron transport chain impairment and autism. It is clear that these findings are too preliminary to be generalized and it is possible that there is only a subsample of children with autism who suffer from electron transport chain.

Nevertheless, these findings are of dual importance. Firstly, they point to a novel pathophsiological element, and secondly, they suggest the potential for novel therapies in autism. Considering the nature of the pathology, it is possible to hypothesize new therapeutic approaches for this subsample of children with autism. It is unclear if this is a trait or state phenomenon, or if it is an enduring or maturational one; there is for example a possibility that the deficits in the levels of electron transport chain complexes in children with autism might reach normal levels in adulthood (Chauhan et al., 2011). It

is also noteworthy that mitochondrial strategies are proposed for other disorders with a mitochondrial element (Nierenberg et al., 2012).

Alternative carrier for shuttling of electron in mitochondrion

Methylene blue (MB) is suggested for the treatment of Alzheimer's disease (Oz et al., 2009). MB passes blood brain barrier and enters into CSF (Peter et al., 2000) and enters the mitochondrion (Oz et al., 2009). Low doses of MB are relatively safe (Oz et al., 2009) and lack nonspecific behavioral adverse effects (Riha et al., 2005). However, MB has hormetic pharmacological effects, whereby low or very high doses causes opposite results (Peter et al., 2000). Very high non-therapeutic doses may produce Heinz body in erythrocytes, and are markers of oxidative damage to hemoglobin (Sills and Zinkham, 1994).

It is well known that methylene blue can carry electrons in the mitochondrial electron transport chain (Rojas et al., 2011; Visarius et al., 1997). As an alternative electron carrier, MB receives electrons from NADH and shuttles them to cytochrome c (Wen et al., 2011). In fact, MB bypasses complex I/III while it does affect the activity of complex II and complex III (Wen et al., 2011).

Oxidized methylene blue is reduced after receiving electrons from a donor. This reduced form can donate electrons to cytochrome c and oxygen. This reduced oxygen is used to produce water. This oxidation-reduction process of methylene blue is

reversible. Moreover, MB decreases superoxide and hydroxyl radical production (Kelner et al., 1988; Salaris et al., 1991).

In addition, low dose MB enhances brain cytochrome c oxidation (Callaway et al., 2004) and decreases oxidant production in mitochondria (Atamna et al., 2008). Therefore, MB plays a potential role as an antioxidant (Rojas et al., 2011). As noted previously, analogous electron transport chain abnormalities are seen in bipolar disorder, and it is noteworthy that methylene blue has shown promise in a double blind trial in that disorder (Naylor et al., 1986). This provides some face validity for trials in autism. However, it needs to be noticed that MB can be reduced by other reductants and its effects on other issues should be considered.

N-acetyl cysteine (NAC) is another potential therapeutic modality. It has positive trial data for depression in bipolar disorder, negative and extrapyramidal symptoms in schizophrenia, cocaine craving, smoking cessation, trichotillomania and gambling (Dean et al., 2011). There are a case report and a single clinical trial of NAC in autism, where in 33 subjects aged 3.2–10.7 years, a significant reduction in irritability was evident (Ghanizadeh and Derakhshan, Under Press; Hardan et al., 2012). NAC has been shown to reduce apoptosis secondary to mitochondrial oxidative stress. NAC reverses direct mitochondrial toxicity in a number of experimental models (Sandhir et al., 2012). Additionally, NAC has been shown to normalise pyruvate and lactate levels, which are mitochondria-associated factors. These data support the presence of mitochondrial dysfunction as an addressable target in autism (Giulivi et al., 2012), and suggests

potential neuroprotective stategies (Berger et al., 2007).It is also suggested that such therapies are initiated as promptly as possible (Berk et al., 2007), as there may be a process of neuroprogression (Berk, 2009) in autism.

Hypothesis

Considering that the activity of the mitochondrial electron transfer complexes I, II, III and IV in autism are lower than the controls (Weissman et al., 2008), that there is increased oxidative stress and ROS production in autism (Ghanizadeh et al., 2012; Zoroglu et al., 2004), and there is a role of shuttling of electrons in mitochondria for neuroprotection (Wen et al., 2011), it is hypothesized that this alternative electron shuttling may decrease the production of ROS induced by lower ETC activity in autism. In addition, since this alternative shutting transfers electrons to cytochorome c, it is expected that the production of ATP will be enhanced. Experimental controlled studies on animal models need to be conducted to test these hypotheses.

Conclusion

The current literature support that electron transport chain is involved in the neurobiology of some children with autism. However, this area deserves further

investigation. Targeting the electron transport chain by bypass augmenting targeted functions is a hypothesized potential treatment approach.

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Figure 1. Flowchart of studies selection process.

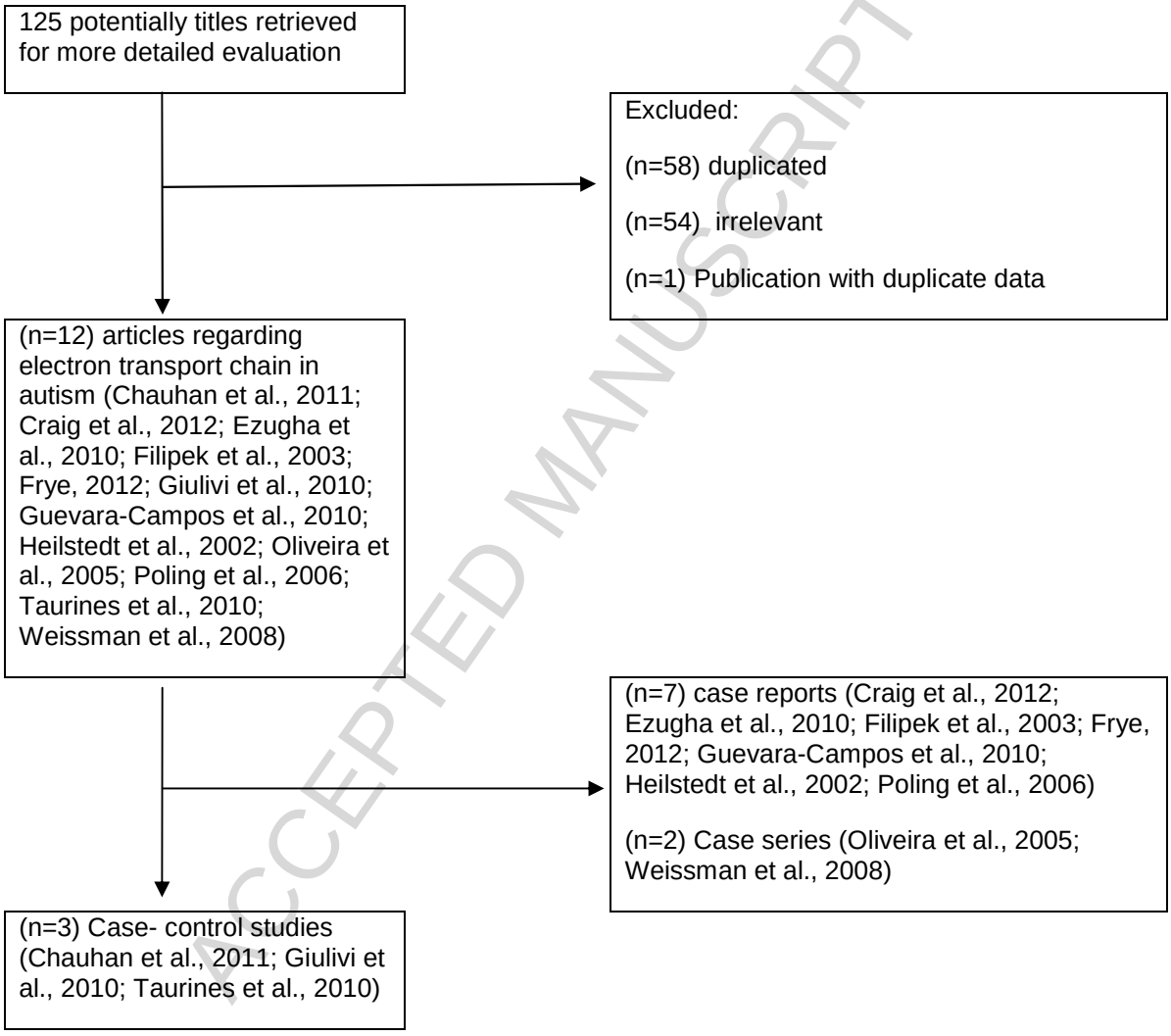

Table 1. The case-control studies met inclusion criteria for this systematic review.

Author, year	complexes	Area	Diagnosis	Findings
(Chauhan et al., 2011)	complexes I, II, III, IV, and V	Cerebellum and the frontal, parietal, occipital, and temporal cortices	Autism	Children aged 4 to 10 years old: lower levels of complexes III and V in the cerebellum ($p < 0.05$), of complex I in the frontal cortex ($p < 0.05$), and of complexes II ($p < 0.01$), III ($p < 0.01$), and V ($p < 0.05$) in the temporal cortex in autism comparing to age-matched control children Adults, ages 14–39 years: No difference between autism and control group.
(Giulivi et al., 2010)	complexes I, III, IV, and V	lymphocytic mitochondria	autism	Complex I activity in lymphocytic mitochondria 6 of 10children with autism was below control range values. The activities of Complex V (4 of 10), and complex IV or cytochrome c oxidase (3 of 10) and complex III only (1 of 10 each) was below control range values.
(Taurines et al., 2010)	expression of the complex I 75-kDa subunit mRNA	Blood	Schizophrenia group and autism spectrum disorders group	The ASD group did not show a significantly altered expression of the complex I 75-kDa subunit mRNA in blood.

Table 2. The case reports and case series studies met inclusion criteria for this systematic review.

Author, year	Diagnosis	Findings
(Craig et al., 2012)	Dravet syndrome, seizures, and features consistent with severe autism	complex IV dysfunction
(Ezugha et al., 2010)	dysmorphic facies, mental retardation, autism, epilepsy, and leg weakness	Buccal swab electron transport chain analysis revealed: severe decrease in complex IV and mild reduction in complex I activity levels.
(Frye, 2012)	Autism spectrum disorder	A marked reduction in complex II and II/III in fibroblasts and complex I/III and II/III in muscle tissue
(Guevara-Campos et al., 2010)	Autistic	A partial deficiency of complexes III and IV of the respiratory chain
(Poling et al., 2006)	Autism	Reduction of cytochrome c oxidase activity, enzymatic activities for complex I and III. Complex IV (cytochrome c oxidase) activity was near the 5% confidence level.
(Filipek et al., 2003)	Autism	complex III activity per mitochondrion was reduced.
(Weissman et al., 2008)	Autism spectrum disorders	The most common ETC disorders: deficiencies of complex I (64%) and complex III (20%).
(Oliveira et al., 2005)	Autistic disorder	5 out of 11 patients were with mitochondrial respiratory chain disorder; most commonly complexes I, IV, and V

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