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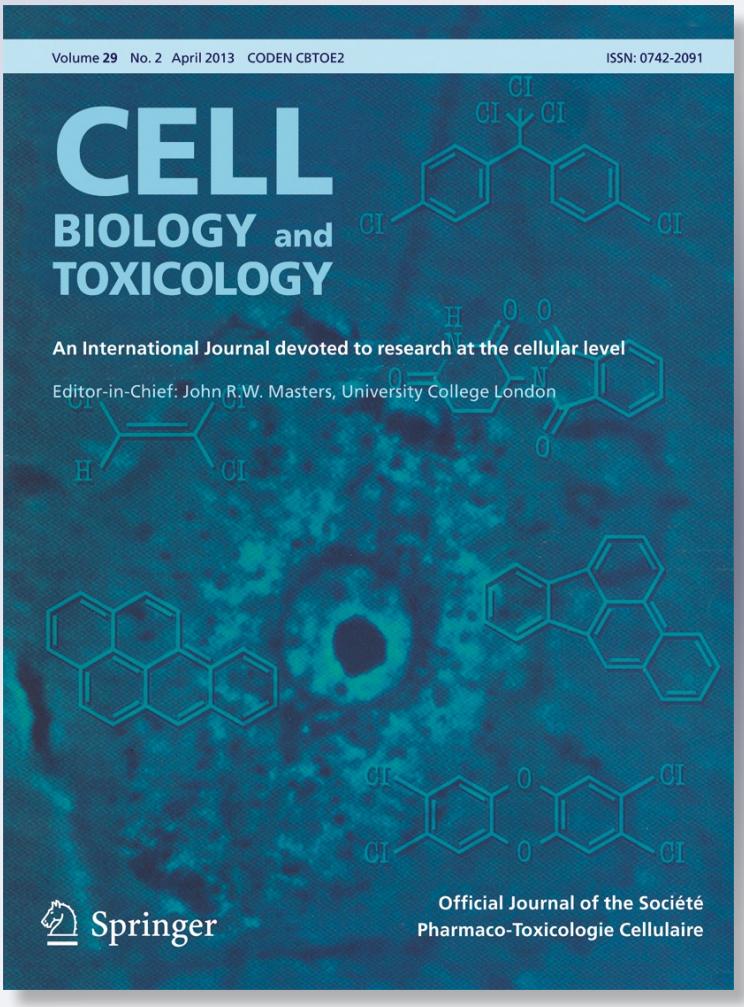

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REVIEW ARTICLE

How aluminum, an intracellular ROS generator promotes hepatic and neurological diseases: the metabolic tale

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Abstract Metal pollutants are a global health risk due to their ability to contribute to a variety of diseases. Aluminum (Al), a ubiquitous environmental contaminant is implicated in anemia, osteomalacia, hepatic disorder, and neurological disorder. In this review, we outline how this intracellular generator of reactive oxygen species (ROS) triggers a metabolic shift towards lipogenesis in astrocytes and hepatocytes. This Al-evoked phenomenon is coupled to diminished mitochondrial activity, anerobiosis, and the channeling of α-ketoacids towards anti-oxidant defense. The resulting metabolic reconfiguration leads to fat accumulation and a reduction in ATP synthesis, characteristics that are common to numerous medical disorders. Hence, the ability of Al toxicity to create an oxidative environment promotes dysfunctional metabolic processes in astrocytes and hepatocytes. These molecular events triggered by Al-induced ROS production are the potential mediators of brain and liver disorders.

Keywords Aluminum toxicity · Reactive oxygen species · Mitochondrial dysfunction · Dyslipidemia · α-ketoacids · Neurological and hepatic diseases

Abbreviations

BADH	Betaine-aldehyde dehydrogenase
BBDOX	γ-butyrobetaine dioxygenase
ETC	Electron transport chain
HDL	High-density lipoprotein
HIF	Hypoxia-inducible factor
HTML	3-hydroxy-N^6-trimethyllysine
ICDH	Isocitrate dehydrogenase
KGDH	Alpha-ketoglutarate dehydrogenase
LDL	Low-density lipoprotein
MDH	Malate dehydrogenase
PHD	Prolyl hydroxylase
ROS	Reactive oxygen species
TCA	Tricarboxylic acid
TML	N^6-trimethyllysine
TMLD	Trimethyllysine dioxygenase
VLDL	Very-low-density lipoprotein

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The environmental toxin aluminum and human exposure

Metal pollution is an ongoing concern as it is the foundation of numerous health problems. Acidification, industrialization, and the utilization of metals in our daily life have all contributed to the elevated metal concentrations in the environment (Gómez et al. 2008; Klein

2005; Exley 2009). The trivalent metal, aluminum (Al), has gained substantial interest due to its increased bioavailability and its negative effect on human health (Krewski et al. 2007). Despite the fact that Al comprises approximately 8 % of the Earth's crust, its insoluble nature has generally ensured its nonbioavailability (Exley 2003). However, there has been a significant increase in the presence of soluble Al due to acidification and anthropogenic activities. Furthermore, it is also present in food additives, pharmaceuticals, and as a flocculent in drinking water (Krewski et al. 2007; Silva et al. 2002; Soni et al. 2001).

Exposure to Al occurs via various routes, including inhalation, ingestion and dermal absorption (Nayak 2002). Due to the abundance of Al in numerous food products (Table 1), its ingestion has been the predominant route of how this metal gains entry into human biological systems, averaging approximately 8 mg/day intake in the general population (Krewski et al. 2007). However, other common sources have also been shown to contribute to this Al burden (Table 2). Although Al may be eliminated effectively via the kidney, it is absorbed at approximately 0.1 % via the gastrointestinal tract, and leads to numerous immediate and long term deleterious effects (Krewski et al. 2007; Priest 2004). Epidemiological studies have shown that Al uptake can proceed via inhalation, primarily through occupational exposure, and the consumption of water treated with Al flocculants (Ferreira et al. 2008; Priest 2004; Moulin et al. 2000; Romundstad et al. 2000; Rondeau et al. 2000; Barnard et al. 2004). The level of Al absorption through the intestine can vary according to age, sex, and diet. Once absorbed, Al has a half-life of several hours in the blood. It is subsequently either eliminated through the urinary tract or distributed throughout the body by the iron-binding protein transferrin (Harris et al. 1996) and accumulates in various organs such as bone, lung, muscle, liver, and brain. The accumulation of Al in these organs appears to be the initiator of a variety of medical conditions (Krewski et al. 2007; Priest 2004).

Table 1 Al content in various food sources (adapted from Soni et al. 2001)

Food	Al concentration (mg/100 g)
Natural cheese	1.57
Processed cheese	29.70
Bran and wheat	1.28
Blueberry muffins	12.80
Pancake mix	6.90
Tortilla flour	12.90
Cornbread	40.00
Cocoa	4.50
Substitute cream	13.90
Spinach	
Boiled	2.50
Canned	1.17
Potatoes	
Cooked	1.08
Baked	2.60
Herbs	
Bay	43.60
Cinnamon	8.20
Oregano	60.00
Black pepper	14.30
Thyme	75.00
Basil	30.80
Celery seed	46.50
Sage	40.40
Baking powder	2,300.00

Al-related diseases

The impact of Al on biological systems has been well-documented and its involvement in skeletal, hematological, and neurological diseases has been widely reported (Nayak 2002). Osteomalacia is one of the skeletal diseases related to Al, caused by defective mineralization of the osteoid matrix, resulting in softening of the bones. Phosphate deficiency, calcium uptake impairment, and dysfunctional osteoblast proliferation are some of the signature effects of Al

Table 2 Al exposure from alternate source (adapted from Yokel et al. 2008)

Source	Al exposure
Antacids	5,000,000 μg/day
Air inhalation	4–20 μg/day
Industrial air inhalation	25,000 μg/day
Antiperspirants	70,000 μg/day
Cigarettes	500–2,000 μg/cigarette
Vaccines	1–8 μg/day
Allergy immunotherapy	7–40 μg/day

toxicity (Gura 2010). The connection between anemia and Al has been established based on the observations that Al exposure can impair intestinal Fe absorption, increase Fe concentration in the serum, and disrupt normal tissue ferritin levels (Klein 2005; Nayak 2002; Rosenlöf et al. 1990). Al causes disruptions to Fe homeostasis by displacing the Fe in transferrin, resulting in its release into the bloodstream. The body Fe control systems mistake the increase in serum Fe levels as the result of an Fe-overload and thus secrete hepcidin to cease Fe uptake of this micronutrient. The net result is a decrease in Fe absorption and the promotion of an anemic state (Ganz 2011; Bignucolo et al. 2012). When the body senses a rise in serum Fe levels, hepcidin is released in an effort to reduce Fe uptake by the intestine and limit the cellular efflux of Fe from hepatocytes, enterocytes, and macrophages (Bignucolo et al. 2012). Hence, Al toxicity may lead to hematological disorders via a hepcidin-mediated process.

Al has also been recognized as a neurotoxin and is implicated in a number of neurodegenerative diseases, such as Alzheimer's disease and encephalopathy (Rondeau et al. 2000; Nakamura et al. 2000; Gorell et al. 2004). Although the causative agents of Alzheimer's disease have yet to be fully delineated, metals, such as copper, zinc, and Al have been proposed to participate in the pathogenesis of this disease (Lovell et al. 1998; Hung et al. 2010; Cuajungco et al. 2000; Flaten 2001; Rondeau et al. 2009; Lukiw and Pogue 2007). The disruption of the intracellular redox environment appears to be an important contributing factor (Christen 2000; Becaria et al. 2006).

Al, a generator of ROS

The main mechanism of Al toxicity involves the disruption of the homeostasis of metals, such as magnesium (Mg), calcium (Ca), and iron (Fe) (Kawahara and Kato-Negishi 2011; Harris et al. 1996). The physical and chemical properties of Al allow it to effectively mimic these metals in their respective biological functions and trigger biochemical abnormalities. Al has been shown to replace Mg and bind to phosphate groups on the cell membrane, DNA and ATP (Tomljenovic 2011). In particular, there is evidence to suggest that nanomolar concentrations of Al can induce genotoxicity in primary human neural cells, promoting the up-regulation of pro-inflammatory and pro-apoptotic genes (Lukiw et al. 2005). However, the effect of Al on Fe homeostasis is the pivotal factor that renders this metal toxic (Ward et al. 2001; Peto 2010; Wu et al. 2012). This interaction generates labile Fe from Fe-containing enzymes and proteins. The intracellular pool of free Fe increases, a situation conducive to the formation of reactive oxygen species (ROS). Indeed, elevated levels of ROS have been shown in various systems exposed to Al (Mailloux et al. 2011; Yuan et al. 2012; Nayak et al. 2010) (Fig. 1). These effects are reversed by antioxidants like *N*-acetyl cysteine (Richards et al. 2011; Zhang et al. 2009). An Al-induced oxidative environment is characterized by increased oxidized lipids, oxidized proteins, and a sharp decrease in mitochondrial activity. Oxidative damage in the brains of animals exposed to Al has been observed (Nehru and Anand 2005; Guo et al. 2009; Li et al. 2012; Praticò et al. 2002). These findings correlated well with in vitro studies, implicating Fe-mediated ROS production under Al stress in nerve tissue (Kaizer et al. 2005; Kaneko et al. 2004, 2007; Ohyashiki et al. 2002; Nehru and Bhalla 2006). The intracellular genesis of ROS in response to an Al challenge in various cellular models has also been reported (Bhasin et al. 2012; Jeffery et al. 1996; Yousef and Salama 2009). Increased lipid peroxidation, decreased membrane fluidity, oxidized high-density lipoprotein, and altered redox status are hallmarks of an oxidative environment, and these dysfunctions are all linked to the Al toxicity (Mailloux et al. 2011; Candan and Tuzmen 2008; Ferretti et al. 2003). Therefore, Al inflicts its toxic influence by creating an intracellular oxidative environment, a situation conducive to major biological complications and diseases.

Al toxicity, ROS, and mitochondrial energy metabolism

As the mitochondrion serves as the power house in most aerobic eukaryotic organisms, dysfunction of this organelle results in diminished ATP synthesis, an effect that has wide ranging cellular implications. Oxidative phosphorylation is the main energy-yielding machinery of aerobic organisms. Since the mitochondria are the most Fe-rich organelle, it is not surprising that the toxicity of Al is acutely felt in this system (Zatta et al. 2000; Wu et al. 2012). Enzymes of the tricarboxylic acid (TCA) cycle, such as aconitase (ACN; EC 3.2.1.3), succinate dehydrogenase (EC 1.3.5.1) and fumarate

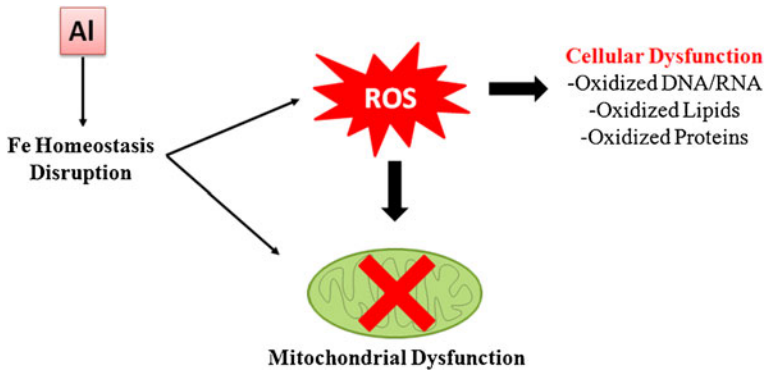

Fig. 1 Al toxicity leads to intracellular free Fe that contributes in generating oxidative stress and mitochondrial dysfunction

hydratase (FUM; EC 4.2.1.2) contain Fe–sulfur (S) clusters and are known to be severely affected by Al (Mailloux et al. 2006). Furthermore, the enzymes involved in the electron transport chain (ETC) including; complex I (EC 1.6.5.3), complex III (EC 1.10.2.2), and Complex IV (EC 1.9.3.1], are laden with Fe–S clusters and hemes (Rouault and Tong 2005). The presence of Al impedes the activities of these complexes, thus sharply limiting ATP production via oxidative phosphorylation. It is interesting to note that both oxidative stress and mitochondrial dysfunction have been linked to the pathogenesis of Parkinson's disease (Taylor et al. 2013).

The Al-triggered ROS formation and reduction in bioavailable Fe render the TCA cycle and oxidative phosphorylation less effective. Indeed, Al-challenged astrocytes and hepatocytes experience a reduced capacity of their ETC activity as revealed by rhodamine tracking (Mailloux et al. 2006). As this trivalent metal has been shown to mimic Fe and generate ROS in vivo, the disruption of the Fe–S cluster is an important route by which Al interferes with the TCA cycle and ETC (Middaugh et al. 2005). This reduction or absence of oxidative phosphorylation leads to a dramatic change in the mitochondrial membrane potential, an event that can be followed by fluorescence microscopy (Fig. 2). The toxic influence of $AlCl_3$ on neuronal cells is also known to impede the ability of the mitochondria to produce energy. In this instance, a marked diminution of complex IV activity appears to be mediated by the reduction in mRNA synthesis of subunit III (Bosetti et al. 2001). The participation of Al-induced monoamine oxidase, an ROS generator, is also known to be responsible for the decrease in mitochondrial energy production (De Marchi et al. 2004). The impairment of metabolic processes in the mitochondria and the decrease of superoxide dismutase (SOD) as a consequence of Al exposure impede this organelle's ability to produce energy via oxidative phosphorylation (Kumar et al. 2009).

An ROS-rich environment promotes anerobiosis

The inability to generate ATP in an oxygen-dependent manner compels these Al-stressed cells to switch their energy production to anaerobic respiration. This alteration leads to the production of ATP by substrate-level phosphorylation, a situation that drastically limits the ATP output of these systems (Mailloux et al. 2006). This process is aided by the stabilization of hypoxia inducible factor-1α (HIF-1α), a transcription factor known to promote adaptation at low oxygen conditions by activating the glycolysis. Hexokinase (EC 2.7.1.1), glyceraldehyde-3-phosphate dehydrogenase (EC 1.2.1.12), pyruvate kinase (EC 2.7.1.40), and lactate dehydrogenase (EC 1.1.1.27) are all up-regulated. This metabolic network enables the cellular systems to fulfill their need for energy, albeit at a sharply reduced rate (Mailloux and Appanna 2007). The dysfunction in normal ATP production has major implications for astrocytes as they depend on a well-maintained structure in order to accomplish their biological tasks in the brain (Lemire et al. 2009; Reichenbach et al. 2009).

The stellate-like morphology is an important contributor to the normal functioning of astrocytes (Reichenbach et al. 2009; Petzold and Murthy 2011). Reduced ATP production can impair many cellular activities, including the morphology of the astrocytes. Particularly, actin polymerization is affected by diminished levels of ATP. Dysfunctional filamentous actin formation alters the morphology of the cell. Indeed, Al-challenged astrocytes adopt a globular structure rather than exhibiting the extended processes observed

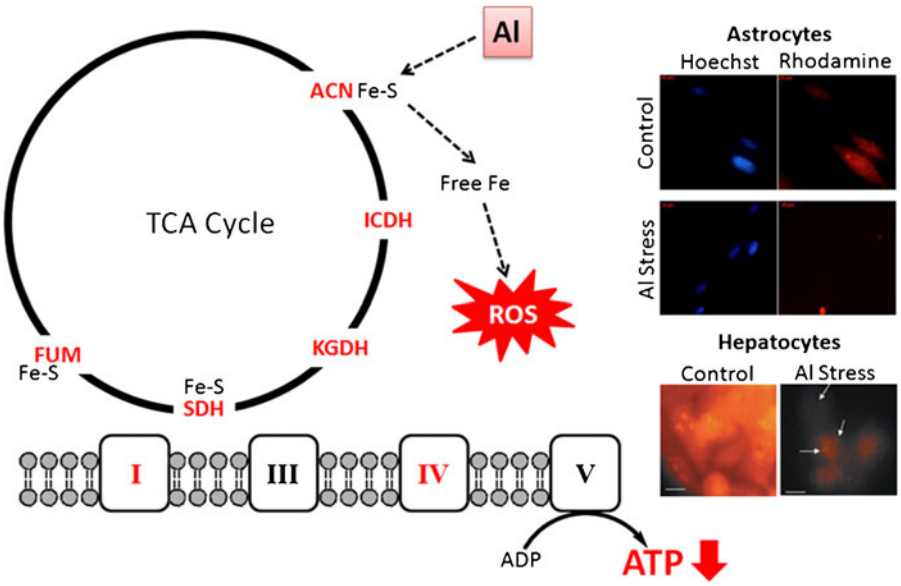

Fig. 2 Disruption of ATP synthesis in the mitochondria. Al displaces Fe in Fe–S clusters in TCA and ETC enzymes impeding ATP production via oxidative phosphorylation. Rhodamine dye demonstrates impaired activity of mitochondria under Al stress. (Note: *red*=downregulation.) *ACN* aconitase, *ICDH* isocitrate dehydrogenase, *KGDH* 2-oxogluatarate dehydrogenase, *SDH* succinate dehydrogenase, *FUM* fumerate dehydrogenase. Hepatocytes *scale bar*=7 μm microscopic images of astrocytes and hepatocytes are adapted from Lemire (2011)

in the control astrocytes (Lemire et al. 2009). These structural changes invoked in response to a disruption in ATP production lead to physiological complications that contribute to the neurological diseases observed under oxidative stress. Indeed, numerous Al-induced neurological diseases may result from dysfunctional astrocytes (Kaur et al. 2006).

ROS, succinate signaling, and carnitine biosynthesis

Although the ROS promoted by Al toxicity severely impedes the TCA cycle, the oxidative environment stimulates the production of NADPH by the activation of NADP-dependent isocitrate dehydrogenase (NADP-ICDH; EC 1.1.1.42) with the concomitant reduction of the NAD-dependent isocitrate dehydrogenase (EC 1.1.1.41). The net result of this metabolic reconfiguration increases the production of NADPH and α-KG, at the same time limiting the formation of the pro-oxidant NADH, thus further reducing the formation of ROS. The ROS stress also inhibits the enzyme α-ketoglutarate dehydrogenase (KGDH; EC 1.2.4.2). Hence, the increase in NADP-ICDH and the reduction in KGDH work in tandem to augment NADPH and α-KG production (Mailloux et al. 2009). The latter is a well-known antioxidant and effectively attenuates ROS with the concomitant production of succinate.

This dicarboxylic acid is an important signaling molecule as it inhibits prolyl-hydroxylase (PHD), an enzyme that mediates the hydroxylation of hypoxia inducing factor-1α (HIF-1α) (Selak et al. 2005). The inability of PHD to hydroxylate HIF-1α helps stabilize this transcriptional factor. Hence, a decrease in TCA cycle activity and the involvement of α-KG in signaling oxidative stress lead to the activation of anaerobiosis, a process associated with limited ROS release (Selak et al. 2005; Mailloux et al. 2009; Mailloux and Appanna 2007). The metabolic shift induced by the Al-triggered ROS enables the cellular system to increase NADPH formation, and to pool α-KG as an antioxidant (Figs. 3 and 4). This molecular scenario limits NADH synthesis and directs ATP synthesis in an anaerobic fashion. However, this survival strategy has major implications for lipid homeostasis. Indeed, the channeling of α-KG to combat ROS has an important ramification for lipid metabolism as this α-ketoacid is crucial for the synthesis of L-carnitine. The synthesis of this nonessential amino acid is dependent on α-KG (Vaz and Wanders 2002). Its production is drastically reduced in Al-stressed cells, a

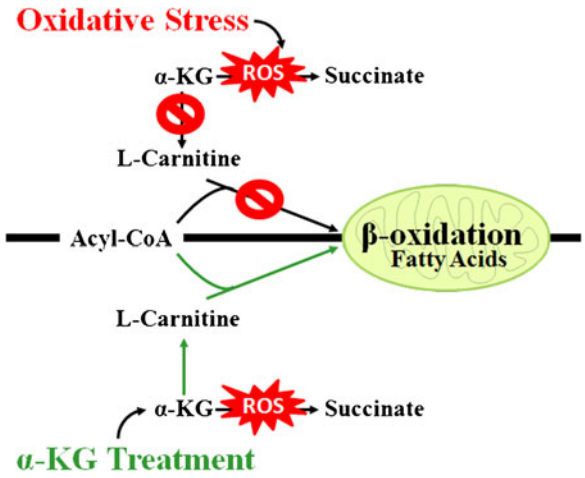

Fig. 3 Impaired β-oxidation of fatty acid under Al-induced oxidative stress. The involvement α-KG in ROS detoxification depletes α-KG for carnitine biosynthesis. However, α-KG supplementation promotes carnitine biosynthesis and allows acyl-CoA transportation to mitochondria for β-oxidation. (Note: *θ*= inhibition and *green*=activation) *α-KG* α-ketoglutarate

situation that impedes the β-oxidation of fatty acids as these moieties cannot be transported into the mitochondria (Vaz and Wanders 2002). This Al-triggered dyslipidemia may lead to a variety of hepatic abnormalities. Indeed in chronic kidney disease resulting from Al overload, there is an accumulation of lipids in the liver and anaerobiosis is known to stimulate lipid production (Mailloux et al. 2007; Li et al. 2006). The elevated concentration of this trivalent metal is known to trigger hepatic disorders. Key hepatic enzymes involved in phosphate metabolism and nitrogen homeostasis are perturbed (Bhasin et al. 2012). There is a diminution in hepatic mass that impairs ion transport. This situation is known to promote cholestasis (González et al. 2009; Buchman et al. 2006).

Disruption of lipid metabolism and ROS

The reduction in L-carnitine production, triggered by a lack of α-KG, promotes lipogenesis and limits the β-oxidation of fatty acids. Enzymes involved in L-carnitine biosynthesis require α-KG as cofactor. During this multi-step process, N^6-trimethyllysine is converted into 3-hydroxy-N^6-trimethyllysine by trimethyllysine dioxygenase (EC 1.14.11.8) in the presence of α-KG. γ-butyrobetaine dioxygenase [EC 1.14.11.1] and betaine-aldehyde dehydrogenase (EC 1.2.1.8) are severely impeded by the Al challenge imposed on astrocytes and hepatocytes (Lemire et al. 2011; Mailloux et al. 2007, 2011). Hence, the diversion of α-KG to combat ROS has the net result of inhibiting β-oxidation, a situation that limits ATP production (Kumar et al. 2008; Mailloux et al. 2006; Sood et al. 2011). The ROS-induced metabolic shift in these cells leads to the production of limited energy via glycolysis and increased lipogenesis. The latter phenomenon results in fat accumulation. Imbalances in energy and lipid production are hallmarks of numerous diseases. Altered lipid metabolism has been linked to various neurological diseases (Adibhatla and Hatcher 2008). Liver diseases and obesity are caused by dysfunctional lipid and energy metabolism, cellular events that are triggered by the pro-oxidant Al (Fig. 3).

α-ketoacids, a potential therapy for ROS-induced diseases

The involvement of α-ketoacids in combating ROS-induced diseases appears to be an intriguing possibility. These natural metabolites play a critical role in

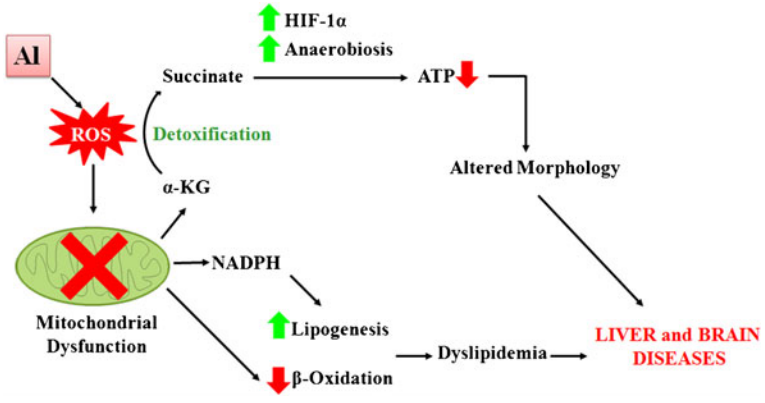

Fig. 4 A schematic depiction of how Al and ROS toxicity may result in liver and brain diseases. *Up arrows* increase; *down arrows* decrease

scavenging ROS, in limiting the production of ROS by impeding NADH formation, in generating a signal molecule that promotes ATP synthesis by substrate-level phosphorylation, and provides metabolites for gluconeogenesis and lipogenesis. Indeed, α-ketoacids have been shown to reverse the toxicity of Al and ROS. A reduction in fat accumulation and increase in mitochondrial energy production are observed in hepatocytes and astrocytes when supplemented with α-ketoacids (Lemire et al. 2011, 2009; Mailloux et al. 2009). α-Ketoacids have been effectively used against a variety of diseases such as cataracts, cardiac ischemic-reperfusion, and ischemia–reperfusion in the brain, where ROS may be the causative agent (Hegde et al. 2007). The use of ketoacids coupled with the administration of a low-protein diet helps mitigate this disorder. α-KG has been shown to be an effective therapy against oxidative stress in rats (Gao et al. 2009). Furthermore, a recent study indicates that the exogenous injection of α-KG limits oxidative stress and enhances β-oxidation of fatty acids. Pyruvate, another α-ketoacid, has a protective effect on neurons subjected to copper-induced cysteine neurotoxicity (Wang and Cynader 2001). This α-ketoacid is also utilized clinically as a cardioprotectant (Kjellman et al. 1997; Mallet et al. 2005). Although the complete therapeutic significance of α-ketoacids has yet to be appreciated, these natural metabolites may provide a safe therapeutic regime to quell oxidative stress, whatever its origin.

Conclusion and therapeutic cues

Al is an omnipresent element that exerts its nefarious influence mainly by perturbing Fe homeostasis, a situation that leads to oxidative stress in living organisms. This challenge inflicted by Al alters the energy metabolism directly through the disruption of the TCA cycle and oxidative phosphorylation. Alterations in metabolic networks impact numerous other biological pathways. The lack of ATP production induces morphological changes in astrocytes. Lipid homeostasis in the liver and the brain is a highly guarded process as lipid moieties play a critical role in energy storage and transmission of neuronal signals. The enhanced secretion of very low-density lipoprotein and low-density lipoprotein in hepatocytes may indicate a possible link between Al toxicity and obesity as obese individuals show symptoms of mitochondrial dysfunction, lack of energy, and abnormal lipid accumulation. Metabolites such as α-KG, pyruvate, and oxaloacetate can play a prominent role in combating ROS stress (Fig. 4). The anti-oxidant attribute of α-ketoacids has been shown in *in-vivo* studies, in clinical settings, and are routinely utilized in various medical interventions. α-Ketoacids have the capacity to be important therapeutics to combat ROS-induced diseases, as they are natural metabolites, their side effects would likely be limited. Their interactions with ROS liberate readily utilizable metabolites or signalling moieties that may further help alleviate the deleterious influence of the oxidizing molecules. Thus, targeting the metabolic dysfunction evoked by Al and ROS toxicity may be crucial in ameliorating diseases promoted by these toxins and ketoacids are indeed excellent candidates for therapeutic leads.

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