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Citation: J Med Discov (2017); 2(4):jmd17040; DOI:10.24262/jmd.2.4.17040

Review

Antimicrobial activity inactivation and toxic immune reactions induce Epilepsy in humans

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The calorie sensitive gene Sirtuin 1 (Sirt 1) determines nitric oxide (NO) homeostasis and immunosenescence relevant to the induction of various chronic diseases in human and other species. Appetite control is essential to Sirt 1 function for preventing adipose tissue transformation (adipocytokine release), non alcoholic fatty liver disease (NAFLD) and the development of epilepsy. Sirt 1 repression by bacterial lipopolysaccharides (LPS) leads to delayed hepatic clearance of anti-microbial drugs with relevance to mitophagy, neuron apoptosis and interference with antimicrobial/antiepileptic drug therapy. Increased absorption of LPS from food/water induces magnesium deficiency with inactivation of antimicrobial/antiepileptic drug therapy. Heat and cold stress alters Sirt 1's role in cell cholesterol dyshomeostasis associated with increased heat shock proteins (HSP) involved with inactivation of antimicrobial proteins and promotion of the cytotoxic immune response. The genetics of immunity that determines immune competence changes over a human's life span and involves the gene Sirt 1 that has antimicrobial properties by its regulation of NO metabolism connected to the immune system, mitophagy and epilepsy.

Keywords: Antimicrobial; Sirtuin 1; immunosenescence; immune; epilepsy; global; mitophagy; heat shock protein; nitric oxide; bacterial lipopolysaccharides; antiepileptic; drug; NAFLD; heat shock gene.

How to cite: Martins IJ, Antimicrobial activity inactivation and toxic immune reactions induce Epilepsy in human. J Med Discov (2017); 2(4):jmd17040; DOI:10.24262/jmd.2.4.17040; Received September 13rd, 2017, Revised October 9th, 2017, Accepted October 13rd, 2017, Published October 15th, 2017.

Introduction

The genetics of immunity have been studied in plants and various species such as *Drosophila* and humans [1, 2]. Immune competence changes over human's life span, which is known as immunosenescence [3]. Aging and defects in the function of the immune system range from defects in the haematopoietic bone marrow to defects in peripheral lymphocyte migration, maturation and function. Human aging and adipose tissue transformation now involve the increased release of adipocytokines [4, 5] that is linked to the global non alcoholic fatty liver disease (NAFLD) epidemic [6, 7] and epilepsy [8-11]. The gene that involves immunosenescence is Sirtuin 1 (Sirt 1) and determines adipose tissue transformation and liver inflammation [5]. Sirt 1 is a nicotinamide adenine dinucleotide (NAD+) dependent class III histone deacetylase (HDAC) that targets transcription factors to adapt gene expression to metabolic activity and the deacetylation of nuclear receptors indicating its critical role in insulin resistance in rodents and man [12].

Sirt 1 is a calorie sensitive gene that is important to the nuclear-mitochondria interaction with deacetylation of transcription factor p53 which is important for the adipose tissue and liver fat metabolism [5]. The p53 transcription factor is involved in immune responses and mitochondrial apoptosis [4] that is critical to the regulation of Sirt 1/p53 immunometabolism and induction of global

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NAFLD [5]. Sirt 1 plays an important role in B cell antibody response and T cell tolerance with relevance to autoimmune and chronic disease [13-16]. Sirt 1 is now one of the major genes involved in immunosenescence and global chronic disease in human [17, 18] and various species [18]. Sirt 1 has antimicrobial properties by its regulation of nitric oxide (NO) metabolism [19] that is now connected to the immune regulation of the mammalian immune system [18]. The global antimicrobial and epileptic drug market is expected to cost 80 billion dollars [20, 21] by the year 2020 with the critical role of Sirt 1 in the maintenance of immunocompetence.

Sirt 1 repression with relevance to Antimicrobial Activity

Repression of Sirt 1 has become of major concern with plasma bacterial lipopolysaccharides (LPS) involved in Sirt 1 repression [22] with interference with NO related immune regulation and global chronic disease [20, 21]. Sirt 1 is essential to antimicrobial drug metabolism [23], caffeine metabolism [24] and xenobiotic metabolism [7] with relevance to its antimicrobial activity (Figure 1). Sirt 1 repression leads to delayed clearance (pharmacokinetic/pharmaco-dynamics) of antimicrobial drugs with relevance to core body temperature and mitophagy [25-27]. LPS is an inhibitor of the apolipoprotein E (apo E) and its neutralization of apo E is involved in the promotion of amyloid beta aggregation [28-30]. LPS interference of apo E and amyloid beta proteins neutralize their role as antimicrobial proteins [31-34]. Elevated plasma LPS levels lead to magnesium deficiency [35, 36] that is now one of major relevance to antimicrobial/antiepileptic drug treatment [37, 38] in various global communities (Figure 1).

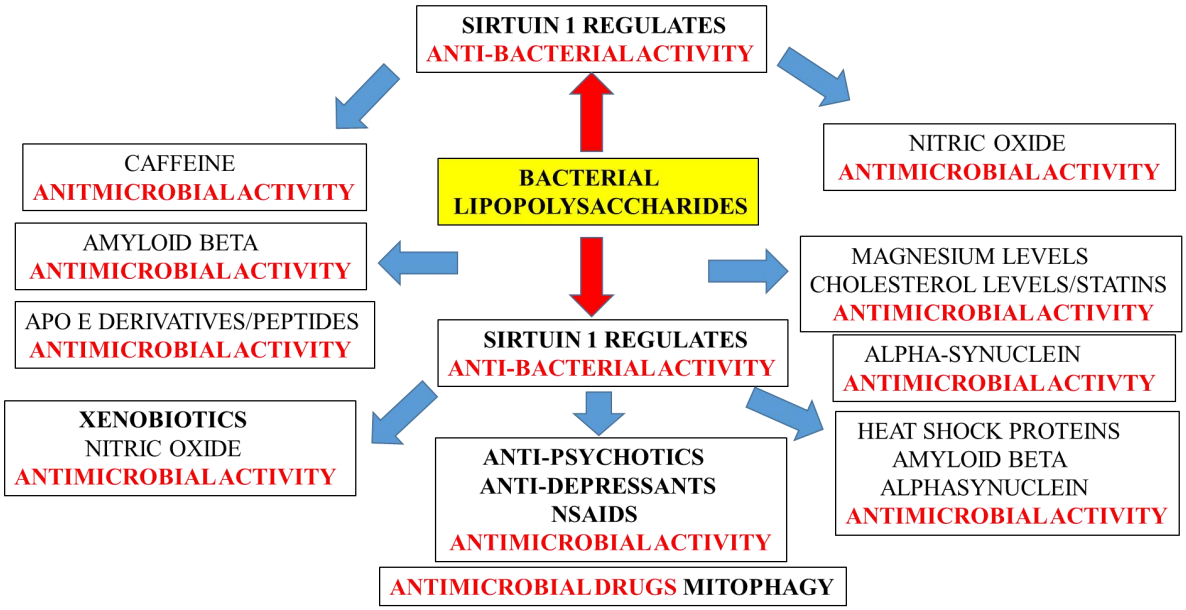

Figure 1. Sirt 1 regulates antimicrobial activity by regulation of nitric oxide homeostasis, antimicrobial proteins, heat shock proteins and hepatic caffeine/xenobiotic metabolism. LPS represses Sirt 1 (hepatic drug metabolism) and apo E/amyloid beta interactions (antimicrobial proteins) and induces magnesium deficiency with relevance to antimicrobial activity.

Heat shock proteins (HSP) induce cytotoxic immune response and override antimicrobial drug activity

Sirt 1 is essential to maintain cell cholesterol homeostasis (Figure 2), such as cholesterol efflux [39], which is important for the binding of antidepressant drugs (antimicrobial activity) [40], antipsychotic drugs (antimicrobial activity) [41], NSAIDs and LPS (sphingomyelin/cholesterol domain) to mammalian cell membranes (Figure 2). Sirt 1 is involved in the metabolism of antimicrobial proteins such as amyloid beta and

alpha synuclein with relevance to cell cholesterol homeostasis [42]. Sirt 1 is now referred to as a heat shock gene and its deacetylation of heat shock factor 1 (Figure 2) is involved with regulation of heat shock protein (HSP) metabolism [43, 44]. HSPs role in alpha synuclein and amyloid beta aggregation is important to antimicrobial activity and mammalian cell immune regulation [45-48]. Elevated HSP levels have been reported in natural killer cell activation with uncontrolled toxic immune reactions [4, 49] and stress responses in epilepsy [50] . Sirt 1 is now connected to epilepsy in man with the Sirt 1 activator resveratrol essential to stabilize epilepticus and epilepsy [51, 52]. Cholesterol lowering agents such as statins have antimicrobial properties with Sirt 1 repression associated with increased cell cholesterol (Figure 2) that may interfere with statins' antimicrobial properties [53].

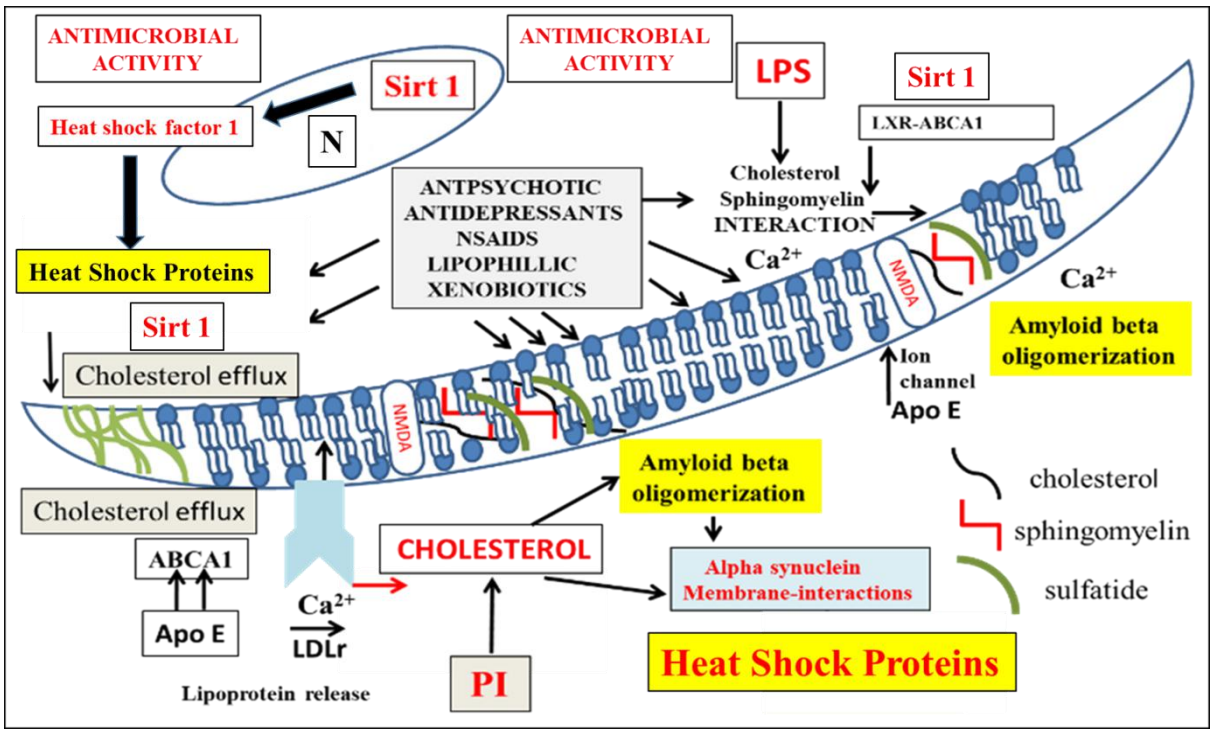

Figure 2. Antimicrobial drugs, antimicrobial proteins (amyloid beta, apo E, alpha synuclein) and heat shock proteins are connected to cell cholesterol levels. Sirt 1 is critical to cell cholesterol efflux with its repression controlled by LPS that is involved in binding to cholesterol:sphingomyelin domains relevant to amyloid beta and alpha synuclein oligomerization. Sirt 1 is important to deacetylation of heat shock factor 1 with relevance to heat shock protein metabolism and antimicrobial activity in neurons and hepatocytes.

Nutrition determines mitochondrial disease, drug therapy and induction of Epilepsy

Appetite control is essential to maintain Sirt 1 regulation of the suprachiasmatic nucleus (SCN) and the circadian rhythm that is defective in NAFLD, obesity and diabetes [54, 55]. Sirt 1 is critical to maintain mitochondrial survival with food restriction essential to maintain mitochondrial biogenesis and reverse NAFLD and diabetes. Appetite regulation and its relevance to various chronic disease is now critical to Sirt 1' role in antimicrobial activity and immune regulation in mammalian cells. Overnutrition overrides appetite control with antimicrobial activity dysregulation now connected to insulin resistance and neurodegenerative diseases in global populations [56].

Food restriction reduces the absorption of LPS that may enter after ingestion of contaminated food and water with relevance to diabetes and neurodegenerative diseases [56-58]. Nutritional diets that contain Sirt 1 activators [24] may reverse NAFLD and epilepsy with relevance cholesterol and HSP metabolism. Consumption of Sirt 1

inhibitors [24] should be avoided that induce NAFLD and inactivate consumption of essential nutrients with relevance to the prevention of NAFLD and epilepsy. Contaminants such as xenobiotics, mycotoxins (patulin) and caffeine may induce mitophagy and impair various therapeutic drugs [25-27] that are essential for treatment of epilepsy.

Epilepsy is a group of neurological disorders with episodes of epileptic seizures (provoked/unprovoked) that involve undetectable periods to long periods of vigorous shaking. Provoked epilepsy with CNS infections [59] involve mitochondrial disease that lead to mitochondrial epilepsy [60] that may be irreversible and connected to the global stroke epidemic [61, 62]. Appetite dysregulation [19] and Sirt 1 dysregulation indicate NO defects and the induction of provoked epilepsy and seizures [63, 64] now relevant to millions of patients in the world (Figure 3) with billion dollar costs to the global community [20, 21]. Sirt 1 repression and its connections to NAFLD and diabetes [5, 7, 12, 24, 35, 36, 39, 44, 58] now implicate between 20-40% of individuals with provoked epilepsy with Sirt 1 inactivation influenced by Western diets and sedentary lifestyles.

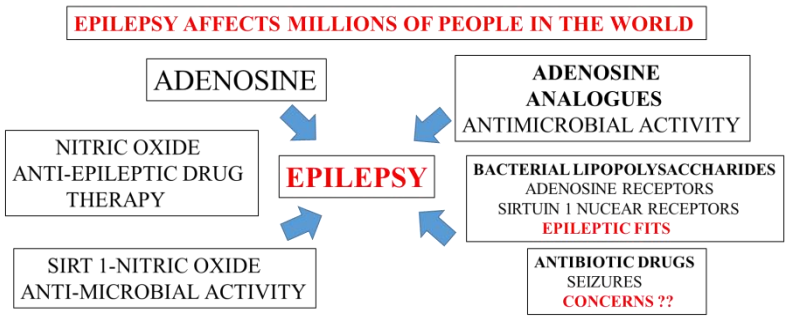

Figure 3. Nutrition is essential to prevent epilepsy that effects millions of individuals in the world. The calorie sensitive gene Sirt 1 regulates NO metabolism with relevance to adenosine treatment and anti-epileptic drug therapy. Overnutrition with Sirt 1 repression (NAFLD) delays hepatic antibiotic drug metabolism such as adenosine analogues, unsubstituted penicillins, fourth-generation cephalosporins, imipenem, and ciprofloxacin with the induction of seizures.

Sirt 1 is now critical to anti-epileptic drug therapy/anticonvulsive actions (Figure 3) and regulation of NO homeostasis [19] control mitochondrial function [54], neuromodulation and neurotransmitter release [65, 66]. Sirt 1 is essential for the prevention of mitochondrial apoptosis and epileptic fits but with increased plasma LPS levels (Sirt 1 repression) in the developing world concerns for decreased antibiotic metabolism may associated with epileptic fits and seizures [67-71]. Adenosine has been used to maintain NO levels and mitochondrial function with relevance to neuromodulation and NO homeostasis (Figure 3) in epileptic conditions [67]. Adenosine analogues [72] have now been shown to have antibacterial activity but increased LPS levels that enter the CSF/ brain [59] may interfere with antibiotic adenosine analogue therapy. LPS binding agents [39] may assist with neutralization of LPS with the prevention of increased transport to the brain and the induction of epilepsy.

Conclusion

Evaluating antimicrobial activity has become important to prevent immune reactions that lead to uncontrolled seizures with emergency and acute stroke. Nutritional regulation of Sirt 1 with relevance to antimicrobial activity in humans has become important to the clinical treatment of epilepsy. Sirt 1 activators need to be consumed to prevent LPS competitive inhibitor effects on Sirt 1 with relevance to the induction of provoked epilepsy. Drug doses of suramin and sirtinol (Sirt 1 inhibitors) should be reduced to stabilize drug treatment of epilepsy. Diets that contain increased palmitic acid and fructose (Sirt 1 inhibitors) induce NAFLD and these nutrients need to be carefully

regulated to maintain antimicrobial activity in man and prevent toxic immune reactions involved in diabetes and provoked epilepsy.

Acknowledgements

This work was supported by grants from Edith Cowan University, the McCusker Alzheimer's Research Foundation and the National Health and Medical Research Council.

Conflict of Interest

None

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