



Peripheral blood *SIRT1* mRNA levels in depression and treatment with electroconvulsive therapy

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Abstract

Sirtuins are a family of nicotinamide adenine dinucleotide (NAD⁺) dependent enzymes that regulate cellular functions through deacetylation of protein targets. They have roles in both the periphery and central nervous system and have been implicated in depression biology. A recent genome-wide association study has identified a locus for major depression in the Sirtuin1 gene (*SIRT1*) and lower blood levels of *SIRT1* mRNA in patients with depression have also been observed in two studies. To our knowledge, no studies have examined the effect of treatment on *SIRT1* levels in patients with depression. We therefore examined *SIRT1* mRNA levels in a well characterised group of patients with depression, compared to healthy controls, and characterised the effects of a course of electroconvulsive therapy (ECT) on peripheral blood *SIRT1* mRNA. Depressed patients ($n = 91$) were matched to healthy controls ($n = 85$) on the basis of age and sex. In line with previous studies, blood *SIRT1* mRNA levels were lower in depressed patients in comparison to controls ($p = 0.005$). However, ECT had no effect on *SIRT1* levels ($p = 0.67$). There was no relationship between baseline pre-ECT *SIRT1* levels and depression severity, change in mood scores, suicidality, depression polarity, presence of psychosis, or response to treatment. There was a trend for a negative association between an increase in *SIRT1* mRNA and a decrease in HAM-D24 scores in ECT responders and remitters. These results indicate that reduced peripheral blood *SIRT1* mRNA could be a trait feature of depression.

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1. Introduction

The sirtuin protein family has recently been implicated in depression. The sirtuins are a group of seven (SIRT1–7) nicotinamide (NAD⁺)-dependent deacetylases, classed as

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type III histone deacetylases (HDAC) (Michan and Sinclair, 2007; Whittle et al., 2007). SIRT1 is mainly found in the nucleus and has peripheral functions in glucose homeostasis, DNA repair, inflammation and apoptosis, as well as aging (Inoue et al., 2017; Oberdoerffer et al., 2008; Rodgers et al., 2005; Tissenbaum and Guarente, 2001; Vaziri et al., 2001). SIRT1 has also been shown to be protective in oxidative stress and have a role in mitochondrial function, possibly through its regulation of peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC1- α), a master regulator of mitochondrial function (Tang, 2016). SIRT1 also functions in the central nervous system (CNS) and regulates circadian rhythms, synaptic plasticity, and memory in animal studies (Asher et al., 2008; Gao et al., 2010; Michan et al., 2010). Additionally, it has roles in neural differentiation and protection and has been implicated in Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's disease (Kim et al., 2007; Pallas et al., 2008).

The first group to identify an association between SIRT1 and depression investigated SIRT1 because of links to circadian rhythm (Kishi et al., 2010). They found an association between a *SIRT1* single nucleotide polymorphism (SNP) and depression in Japanese patients with major depressive disorder (MDD; $n = 450$) but found no association between this SNP and antidepressant response. A subsequent genome-wide association study linked *SIRT1* to MDD, identifying a locus in the *SIRT1* gene in Han Chinese women with recurrent depression (5303 cases; 5337 controls) (Converge Consortium, 2015). More recently, suicidal behaviours and thoughts in bipolar disorder patients ($n = 180$) have been associated with a *SIRT1* gene SNP (Nivoli et al., 2016).

Animal studies have linked SIRT1 to depression but with conflicting results. One of the first studies showed that mice lacking functional SIRT1 are less anxious than wild-type littermates and less susceptible to depressive-like behaviours (Libert et al., 2011). In contrast, chronic stress reduces *Sirt1* mRNA, SIRT1 activity, and protein levels in a mouse model of depression (Abe-Higuchi et al., 2016). They also showed that SIRT1 inhibition leads to a depressive phenotype, whereas SIRT1 activation inhibited a chronic stress-induced depressive phenotype. Resveratrol, a polyphenol antioxidant found in red wine and fruit skins, is a SIRT1 activator (Li et al., 2017a). It has been shown to ameliorate depressive effects in the Wistar-Kyoto rat model of depression (Hurley et al., 2014) and counteract a lipopolysaccharide-induced depressive phenotype in mice (Liu et al., 2016).

In humans, two studies have demonstrated reduced peripheral blood *SIRT1* mRNA levels in depression. The first examined all seven sirtuin genes and found *SIRT1*, *SIRT2* and *SIRT6* mRNA to be reduced in a small group of MDD ($n = 20$) and bipolar depressed ($n = 12$) patients compared to controls ($n = 28$), and also that patients in sustained remission had similar *SIRT1* mRNA levels to controls (Abe et al., 2011). A second study demonstrated reduced blood *SIRT1* mRNA levels in a larger group of MDD patients ($n = 50$) from Shanghai compared to controls ($n = 50$), and this was confirmed in a separate group of MDD patients ($n = 635$) (Luo and Zhang, 2016). However, to our knowledge no studies have assessed the effects of acute treatment on blood *SIRT1* mRNA levels in depression, or if *SIRT1* levels are associated with clinical outcomes.

Electroconvulsive therapy (ECT) is the most effective treatment for severe depression but its mechanism is not fully understood (Sienaert, 2014). Electroconvulsive stimulation (ECS), the animal model equivalent of ECT, has been linked to neuroplasticity mechanisms (Schloesser et al., 2015) and ECT has been shown to increase hippocampal volume in human imaging studies (Wilkinson et al., 2017). A recent study showed that a single ECS increases *Sirt1* mRNA levels in mouse hippocampus and hypothalamus (Chung et al., 2013), and ECS has been reported to induce histone modification of hippocampal genes (Tsankova et al., 2004). As SIRT1 is a histone deacetylase, and may have roles in synaptic plasticity, it could be linked to the mechanism of action of ECT. Finally, we recently identified two microRNAs (miR-126-3p and miR-106a-5p) that were elevated in psychotic depressed patients and that returned to control levels following ECT (Kolshus et al., 2017). Of note, *SIRT1* is a shared target of these two microRNAs.

Together, the above findings suggest a role for SIRT1 in depression and treatment response. Our primary aim was to examine *SIRT1* mRNA levels in patients with depression and controls, and characterise the effects of ECT on peripheral blood *SIRT1* mRNA. We hypothesised that *SIRT1* levels would be lower in depression and be altered following ECT. As a secondary aim we explored differences in depression subtypes and associations between *SIRT1* mRNA levels and clinical outcomes.

2. Experimental procedures

2.1. Human participants

This study included participants recruited as part of the EFFECT-Dep Trial (Enhancing the Effectiveness of ECT in Severe Depression, ISRCTN23577151) (Semkovska et al., 2016) that took place in St Patrick's Mental Health Services, Dublin (www.stpatricks.ie). The study was approved by the St. Patrick's University Hospital research ethics committee and written informed consent was obtained from all participants. This was a pragmatic, randomised, patient- and rater-blinded, non-inferiority trial. To be eligible, participants were over 18 years old and referred for ECT for a major depressive episode as diagnosed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1) (First et al., 1995). Patients were also assessed using the Hamilton Depression Rating Scale 24-item version (HAM-D24) (Beckham and Leber, 1985) and had a score ≥ 21 . Exclusion criteria included a history of schizophrenia, schizoaffective disorder, dementia; alcohol or substance abuse in the previous six months; involuntary status; inability or refusal to provide consent. Patients remained on their regular medication throughout the trial. Unilateral or bitemporal ECT was administered twice-weekly as previously described (Semkovska et al., 2016). Response to ECT was defined as a $\geq 60\%$ reduction in baseline HAM-D24 and a score ≤ 16 . For remission status a patient had to have a $\geq 60\%$ reduction in baseline HAM-D24 and a score ≤ 10 for two consecutive weeks. Fasting blood samples were collected 07.30-09.30 on the morning of the first ECT and 1-3 days after the final treatment.

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