Journal of Affective Disorders 190 (2016) 137–142

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Plasma apolipoprotein E and severity of suicidal behaviour

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ARTICLE INFO

Article history:
Received 13 April 2015
Received in revised form
21 August 2015
Accepted 10 September 2015
Available online 22 October 2015

Keywords:
Suicide attempt
Apolipoprotein E
Childhood adversity
Cholesterol
Stress

ABSTRACT

There is evidence for association between low cholesterol levels and suicidal behaviour. Since apolipoprotein E (ApoE) is involved in the cholesterol metabolism in both the periphery and in the central nervous system; it may be of particular interest in the neurobiology of suicidal behaviour. Furthermore, hypothalamic–pituitary–adrenal (HPA) axis function, one of the main biological systems implicated in both suicidal behaviour and early-life adversity, affect ApoE levels. Very few studies have assessed plasma ApoE in relation to suicidal behaviour. The purpose of this study was to investigate levels of ApoE in plasma in relation to the severity of suicidal behaviour and life-time adversity in the form of exposure to interpersonal violence in suicide attempters. A total of 100 suicide attempters (67 women and 33 men) were enroled in the study. Information on earlier suicide attempts and age at onset of suicidal behaviour was gathered using the Karolinska Suicide History Interview. The Karolinska Interpersonal Violence Scale was used to assess exposure to interpersonal violence. Plasma ApoE was measured by immunonephelometry according to accredited routines. Patients with at least one earlier suicide attempt had significantly higher ApoE levels compared to suicide attempters debuting with suicidal behaviour at inclusion in the study. A higher number of earlier suicide attempts was significantly correlated with higher plasma ApoE levels. Age at onset was significantly negatively correlated with ApoE after adjusting for age. ApoE showed a significant positive correlation with exposure to interpersonal violence as a child in male suicide attempters. *Our findings indicate that ApoE may be related to stress and trauma and the temporal severity of suicidal behaviour.*

1. Introduction

Suicide and suicidal behaviours share a complex multifactorial aetiology and result from the interaction of both distal and proximal factors. Distal factors, such as early-life adversity, alter the regulation of emotional and behavioural traits by epigenetic modification of genes, whereas proximal factors, such as substance abuse and serious life events, may precipitate suicidal behaviour (Pompili et al., 2011; Turecki, 2014). While psychiatric illness is a risk factor for suicide and suicidal behaviour, its predictive value is low and the biomarkers are few in number (Coryell and Schlesser, 2007; Mann and Currier, 2007).

A biomarker of potential interest with regard to suicidal behaviour is apolipoprotein E (ApoE), which is an important agent in cholesterol metabolism. There is evidence for association between low cholesterol levels and suicidal behaviour in clinical and epidemiological studies (Ainiyet and Rybakowski, 2014a; Partonen et al., 1999). Since ApoE is involved in the transport and uptake of cholesterol, lipoproteins and triglycerides in both the periphery and in the central nervous system (Dietschy and Turley, 2004), it may be of particular interest in the neurobiology of suicidal behaviour.

ApoE, coded from a gene located on chromosome 19, is a glycoprotein containing 299 aminoacids (Paik et al., 1985; Rall et al., 1982). It has three major isoforms, ApoE2, ApoE3 and ApoE4. ApoE, not only involved in the lipoprotein metabolism, plays also a role in cognitive function and immune regulation (Mahley and Rall, 2000). While the majority of ApoE is produced by the liver, most cells retain the capacity to produce ApoE locally. ApoE binds to chylomicrons and very low density lipoprotein (VLDL)-particles and facilitates the uptake of exogenous cholesterol. It also takes part in redistribution and excretion of cholesterol, mainly through binding to high density lipoprotein (HDL) particles (HDL with ApoE) which also influence influx and efflux of cholesterol in the cells. Furthermore, It's also involved in local redistribution of cholesterol in organs; a "paracrine" aspect. This function is especially important in cases of stress or injury, where apoE modulates local uptake, storage and release of cholesterol from macrophages or astrocytes (Mahley and Rall, 2000).

The presence of ApoE in the CNS is crucial for the formation of

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http://dx.doi.org/10.1016/j.jad.2015.09.024
0165-0327/

synapses and prevention of neuronal death and is important for axonal growth, as well as for immunoregulation (Hauser et al., 2011; Mahley et al., 2009). In normal circumstances, ApoE in the brain is produced by astrocytes, with neurons being the main recipients (Boyles et al., 1985). ApoE secretion is increased during periods of increased cellular stress or injury and can then also be expressed by neurones and microglia (Kim et al., 2009; Linton et al., 1991; Mahley et al., 2009).

ApoE has been found to play a role in cognitive adaptability as defined by spatial learning in mice (Oitzl et al., 1997) and to be involved in neuronal restructuring and recuperation after brain trauma (Mahley and Huang, 2012; Samatovicz, 2000). While there is a theoretical basis for ApoE being involved in adaptation and recovery after psychiatric illness or trauma, studies on the relationship between ApoE and psychiatric illness, which have focused almost exclusively on genotyping isomers, have generated ambiguous results (Gibbons et al., 2011). Interestingly, ApoE has also been shown to play a significant role in hypothalamic–pituitary–adrenal (HPA) axis activity and immune regulation (Raber et al., 2000), both biological systems being implicated in both suicidal behaviour and early-life adversity (Isung et al. 2014; Jokinen et al., 2007; Turecki, 2014).

However, research evaluating the association between ApoE and suicidal behaviour is scarce. In a study on ApoE in suicide attempters, Baca-Garcia et al. (2004) found no differences in plasma levels of ApoE between suicide attempters and healthy controls. To our knowledge, this is the only study that has investigated plasma ApoE in relation to suicide attempts.

The purpose of this study was to investigate levels of ApoE in plasma in relation to the severity of the suicidal behaviour phenotype, characterized by the number of earlier suicide attempts and age of onset of suicidal behaviour, as well as in relation to lifetime adversity in the form of exposure to interpersonal violence in suicide attempters.

Our hypothesis was that repeated suicide attempts, as well as exposure to interpersonal violence, may be regarded as markers of exposure to stress, which in turn may lead to increased levels of ApoE in plasma through activation of the hypothalamic–pituitary–adrenal (HPA)-axis.

2. Experimental procedures

2.1. Study setting

Patients having their clinical follow-up after an attempted suicide at the Suicide Prevention Clinic at the Karolinska University Hospital were invited to participate in the study on biological and psychological risk factors for suicidal behaviour. Inclusion criteria were a recent suicide attempt (time limit of 1 month), age 18 years or older and a fair capacity to communicate verbally and in writing in the Swedish language. Exclusion criteria were schizophrenia spectrum psychosis, dementia, mental retardation and intravenous drug abuse. A suicide attempt was defined as a self-destructive act with some degree of intent to die assessed with the Freeman scale (Freeman et al., 1974). This definition is in line with the current nomenclature in suicidology (Silverman et al., 2007). Patients were recruited during 2001–2005. The Regional Ethics Review Board in Stockholm approved the study protocol (Dnr. 00-194 and Dnr: 2013/917-32) and the participants gave their written informed consent to participate.

2.2. Patients

During the study period, 258 patients (169 women and 89 men) from the catchment area attempted suicide and came into contact with the Suicide Prevention Clinic. Sixty-one patients met the above-mentioned exclusion criteria, 50 declined to participate in the study and 47 were not chosen to participate for such reasons as initial refusal to have a clinical follow-up, moving to another part of the country or because of a holiday period. A total of 100 suicide attempters (67 women and 33 men) were enroled in the study. The mean age of the patients was 34 years (SD = 12.4; range 18–67), with no difference between men and women. The participants were interviewed by a trained psychiatrist using the SCID I research version interview to establish the diagnosis as assessed by DSM-IV (First et al., 1997). Trained clinical psychologists established Axis II diagnoses by DIP-I interviews (Ottosson et al., 1998). All self-rating scales were completed under the supervision of a research nurse.

Eighty-six percent of the participants had at least one current Axis I psychiatric diagnosis (71% met the criteria for mood disorders, 5% for adjustment disorders, 6% for anxiety disorders, 4% for diagnosed alcohol abuse). Regarding comorbidity, 25% had a comorbid anxiety disorder, 12% had a comorbid substance-related disorder (mostly alcohol dependence) and 4% had a comorbid eating disorder (bulimia nervosa). Nearly one third (28%) of the patients met the criteria for a personality disorder.

2.3. Assessments

The *Karolinska Self Harm History Interview* was used to collect information on earlier suicide attempts and age at the onset of suicidal behaviour. *The Karolinska Self Harm History Interview* contains detailed questions on actual suicide attempt, eliciting factors, wishes and expectations, contact with health care prior to attempt, earlier suicide attempts, and family history of suicide as well as questions on non-suicidal self-injury. The number of earlier suicide attempts is divided into four categories: (1) only one suicide attempt, (2) two suicide attempts, (3) 3–5 suicide attempts, and (4) more than five suicide attempts.

The *Karolinska Interpersonal Violence Scale (KIVS)* (Jokinen et al., 2010) contains four subscales assessing exposure to violence and expressed violent behaviour in childhood (6–14 years of age) and during adult life (age 15 or older). The ratings are based on a semi-structured interview. The scoring ranges between 0 and 5 for all four subscales. In this study, trained clinicians performed and assessed all interviews and ratings. The KIVS scale was validated against several rating scales measuring aggression and acts of violence and the inter-rater reliability of the KIVS subscales was high ($r > 0.9$) (Jokinen et al., 2010).

2.4. Plasma apolipoprotein E analysis

We obtained plasma samples for 74 out of 100 patients. Venous blood was drawn and the samples were frozen and stored in aliquots at −70 °C or below until analysed. No prior thawing of the frozen plasma samples had been carried out. All analyses were performed according to accredited routines by the Karolinska Laboratory at Karolinska University Hospital Huddinge. fS-Apolipoprotein E was analysed by immunonephelometry using BN ProSpec (http://www.healthcare.siemens.com/plasma-protein/systems/bn-prospec-system/technical-specifications) after the addition of specific antibodies. Immunonephelometry measures the scattering of light caused by immune complexes. Concentrations are calculated as the difference in absorbed light between the two measurements (Weisweiler and Schwandt, 1983). Samples were diluted 1:5, after which concentrations of 0.01–0.19 g/l (10–190 mg/l) were calculated, and after a second dilution of 1:20, concentration intervals of 0.04–0.76 g/l (40–760 mg/l) were calculated. Measurements ('fixed-time') were done at 7.5 s and at 6 min, after mixing with antiserum. The increase in light intensity