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Research paper

Glycogen synthase kinase-3β genetic polymorphisms and insomnia in depressed patients: A prospective study

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ABSTRACT

Background: 80–90% of patients with Major Depressive Episode (MDE) experience insomnia and up-to 50% severe insomnia. Glycogen Synthase Kinase-3β (GSK3B) is involved both in mood regulation and circadian rhythm. Since GSK3B polymorphisms could affect protein levels or functionality, we investigated the association of GSK3B polymorphisms with insomnia in a sample of depressed patients treated with antidepressants.

Methods: In this 6-month prospective real-world treatment study in psychiatric settings (METADAP), 492 Caucasian patients requiring a new antidepressant treatment were included and genotyped for five GSK3B Single Nucleotide Polymorphisms (SNPs) (rs6808874, rs6782799, rs2319398, rs13321783, rs334558). Insomnia and MDE severity were rated using the Hamilton Depression Rating Scale (HDRS). Bi- and multivariate analyses were performed to assess the association between GSK3B SNPs and insomnia (main objective). We also assessed their association with MDE severity and HDRS response/remission after antidepressant treatment.

Results: At baseline severe insomnia was associated with the GSK3B rs334558 minor allele (C+) [OR = 1.81, CI95%(1.17–2.80), p = 0.008]. GSK3B rs334558 C+ had greater insomnia improvement after 6 months of antidepressant treatment (p = 0.007, β = 0.17, t = 2.736). No association was found between GSK3B SNPs and MDE baseline severity or 6-month response/remission.

Conclusion: GSK3B rs334558 was associated with insomnia but not with MDE severity in depressed patients. Targeting GSK3B in patients with MDE and a severe insomnia could be a way to improve their symptoms with greater efficiency. And it should be further studied whether the GSK3B-insomnia association may fit into the larger picture of mood disorders.

Introduction

Circadian rhythms are impaired in Major Depressive Episodes (MDE) and in euthymic periods of Major Depressive Disorder (MDD) (Lam, 2008, Duarte Faria et al., 2015). Eighty to 90% of patients with MDE have insomnia (Franzen and Buysse, 2008) and up to 50% have severe insomnia (Costemale-Lacoste et al., 2017). Insomnia may be an endophenotype in MDE. Moreover, while sleep is also regulated by non-circadian processes it could be considered as a clinical marker of circadian rhythm.

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Glycogene synthase kinase-3 (GSK-3) is an ubiquitous kinase involved in many cellular physiological pathways and in circadian rhythms (Beurel et al., 2015). The Glycogene Synthase Kinase-3 isoform β (GSK3B) is a molecular candidate in physiopathology of mood disorders (Gould et al., 2006; Li and Jope, 2010; Pardo et al., 2016). In line with these findings, most of the treatments acting on mood disorders influence GSK3B activity through cellular pathways (Li and Jope, 2010). Moreover, an effect on interaction stability regulation by phosphorylation of two major clock proteins (Circadian Locomoter Output Cycles protein Kaput (CLOCK) and Brain and Muscle Arnt-Like protein-1 (BMAL1)) by GSK3B has been shown (Beurel et al., 2015). Besides, GSK3B showed an interaction with most of the clock proteins such as, PERIOD (Iitaka et al., 2005; Kaladchibachi et al., 2007; Leloup and Goldbeter, 2011; Li et al., 2012), CRYPTOCHROME (Harada et al., 2005; Kurabayashi et al., 2010) and REV-ERB alpha (or NR1D1 _ Nuclear Receptor subfamily 1 group D member 1) (Yin et al., 2010; Besing et al., 2015). Thus, GSK3B could be considered as a component of the biological clock which drives circadian rhythms (Besing et al., 2015).

Moreover, studies of pharmacologic inhibition of GSK3B protein in mammals found impaired circadian rhythms. Hence, Lavoie et al. (Lavoie et al., 2013) demonstrated that the reduction of GSK3B expression in a model of haploinsufficiency (GSK3B + /-) mice lengthened the circadian locomotor activity period as compared to Wild Type mice. Moreover, GSK3B knock-in mice is a mouse model of hyperactivity during the circadian period (Mines et al., 2013). Conversely, pharmacologic inhibitors of GSK3B reverse the effect of genetic (Mines et al., 2013) or pharmacologic induction of hyperactive behaviours (Miller et al., 2009; Beaulieu et al., 2004).

Despite this evidence linking MDD and circadian rhythms, no study in depressed patients assessed GSK3B as a clock protein during MDE.

In humans, GSK3B single nucleotide genetic polymorphisms (SNPs) may affect protein expression or actions (Beurel et al., 2015). Indeed, a functional SNP with effect in the promotor (rs334558 or -50T/C) could alter GSK3B expression in lymphocyte cell lines of Caucasian patients with Parkinson disease (Kwok et al., 2005). Indeed, the T allele had greater transcriptional strength than the C allele.

Our hypothesis was that GSK3B acts on circadian rhythms during MDE. So, GSK3B SNPs could be associated with particular insomnia profiles during MDE. Thus, we investigated the link between GSK3B SNPs and insomnia in patients with MDD and a current MDE.

Methods

Design

This study is based on the METADAP cohort, a 6-month prospective real-world treatment study in psychiatric settings. Patients with a diagnosis of MDD and a current MDE were assessed at the beginning of antidepressant (AD) drug treatment, and 1, 3 and 6 months later (Corruble et al., 2015). Clinical assessments were performed blind to genotyping results. This study was registered by the French National Agency for Medicine and Health Products Safety and the Commission Nationale de l'Informatique et des Libertés, was approved by the Ethics Committee of Paris-Boulogne, France, and conformed to international ethical standards (ClinicalTrials.gov identifier: NCT00526383).

Patients

Six hundred and twenty-four in- or out-patients, aged 18–65 years, with a diagnosis of MDD based on the Mini International Neuropsychiatric Interview with a current MDE and need for switch of AD drugs were included in the METADAP cohort. Among these 624 patients, 544 were genotyped. Four hundred and ninety-two patients (90%) were Caucasians (two Caucasian parents, recorded by self-reports). Only Caucasian subjects were included in the genetic association study. A minimum depression score of 18 on the 17-item Hamilton Depression Rating Scale (HDRS) was required to ensure that patients qualified for current MDE. To be included, patients required the initiation of a new AD. This clinical decision, the drug and its dose, were left to the treating psychiatrist, using 'real world' treatment options. Patients with DSM-IV TR bipolar disorders, psychotic disorders, current substance abuse or dependence, pregnancy, breast feeding, organic brain syndromes or unstable medical conditions were excluded. Patients receiving antipsychotics or mood stabilizers before inclusion and/or for 4 months or more during the last year were excluded. Antipsychotics, mood stabilizers and stimulant were not permitted during the study. Benzodiazepines, at the minimum effective dose and duration were allowed. Psychotherapies were permitted.

All patients signed a written informed consent for study participation and for genetic analyses.

Antidepressant drugs

An AD monotherapy was chosen by clinicians using "real world" treatment options. In this study, ADs belonged on one of four main AD classes (Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin and Noradrenalin reuptake inhibitor (SNRI), tricyclics and others). Of the 492 Caucasian patients, SSRI (n = 198) and SNRI (n = 199) were the two most prescribed AD drugs.

SNP selection and genotyping

Four SNPs (rs334558, rs6808874, rs13321783, rs2319398) were initially selected in METADAP study based on Tsai et al. results who showed an association of these SNPs with AD treatment response (Tsai et al., 2008). GSK3B rs6782799 was selected based on the results of Yang et al. evidencing an association between this polymorphism and MDD risk (Yang et al., 2010). Moreover, rs334558 have shown a transcriptionnal effect on GSK3B expression and more positive results than others (Kwok et al., 2005; Adli et al., 2007; Chen et al., 2015; Saus et al., 2010; Yoon and Kim, 2010; Liu et al., 2014).

A sample of 5 mL of whole blood was collected at baseline. Genomic DNA was extracted from circulating blood leukocytes by Gentra® Puregene® Blood Kits, following the manufacturer's protocol (Qiagen, MN, USA) and stored at −20°C. Five GSK3B SNPs (rs6808874, rs6782799, rs2319398, rs13321783, rs334558) were genotyping by the IntegraGen company (Evry, France) using the Fluidigm® BioMarkTM HD system (Fluidigm Corporation, CA, USA). Some genetic results were not available depending on each SNP, ranging from 60 to 68 patients, due to a lack of amplification and low call rates. Allelic repartition showed that 3/5 SNPs (rs6808874, rs2319398, rs334558) were in Hardy–Weinberg equilibrium (Table 1).

Clinical assessment

2.5.1. Major depressive episode severity

The HDRS was rated by trained clinicians at baseline, and during the following times at 1, 3 and 6 months after the beginning of a new AD. Baseline severity was measured based on the HDRS-17 items total score.

2.5.2. Insomnia

Insomnia assessment was based on the 3 items of the Hamilton Depression Rating Scale 17 items (HDRS) scale: difficulty falling asleep, difficulty staying asleep, and early morning awakenings (items 4, 5 and 6 respectively). Each item was rated from 0 to 2 depending on the symptom presence and severity. The total insomnia score was the sum of the 3 item scores (0-6) (Manber et al., 2005). Insomnia improvement was the difference between total insomnia score at baseline and at each time point (1, 3 and 6 months). Three variables were calculated: M0-M1, M0-M3 and M0-M6 insomnia score.