Interaction of Melatonin and MTNR1B Genotype on Glucose Control - Study 1

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Study Protocol

Using a randomized, double-blind, placebo-controlled, cross-over design, we aim to determine the effects of 5 mg melatonin oral administration and its interaction with *MTNR1B* (encodes the high-affinity melatonin receptor 1B) genotypes on disposition index (DI), first-phase insulin release, insulin sensitivity, and glucose tolerance, using a high-frequency intravenous glucose tolerance test (IVGTT) performed in the afternoon. Both carriers of the *MTNR1B* risk SNP and non-carriers will be randomized to the order of conditions (melatonin/placebo) in a crossover design. The Internal Drug Services will follow a randomization scheme in which participants will be block-randomized (block size equals 2) into two treatment orders (melatonin/placebo or placebo/melatonin). Men and women will be randomized equally between the melatonin and placebo groups. Participants undergo one 5-day in-laboratory stay, during which participants maintain their habitual sleep/wake cycle as they have been doing for the 2-3 weeks prior to each admission. Following each admission and after a baseline day and night, participants receive 5 mg of melatonin or placebo during Wake Period (WP) 2, ~1h before the glucose infusion of IVGTT (ensuring peak levels at the start and high levels throughout the 3-h IVGTT). After two washout days and nights, on WP4, participants receive the opposite treatment to the one received on WP2. IVGTT's begin ~1h after melatonin/placebo administrations, and a mixed meal test begin ~1h after IVGTT ends. This approach allows us to assess an unresolved question which is whether melatonin and its interaction with the *MTNR1B* risk variant have a more profound impact on peripheral insulin sensitivity or, by contrast, on pancreatic insulin secretion. Investigational Drug Services (IDS) block-randomize participants (block size 2) into two treatment orders (melatonin/placebo or placebo/melatonin). In addition to the research participants, all personnel who have contact with the participants or with the endpoint assessment are blinded (all investigators, recruitment personnel, technicians, nurses, and physicians).

Statistical methods

We apply mixed model analysis on outcomes deduced from FSIGT, with melatonin/placebo as fixed factor, and individual as random factor (DI, insulin sensitivity, beta-cell function). To test the interaction effect with *MTNR1B* genotype, we use the same model, but include genotype (carriers vs. non-carriers) as a second fixed factor. Although genotype groups be matched for sex, age, and BMI, we test whether any of these factors are significant covariates. We also test for any order effects. Outcome variables exhibiting non-normality will be transformed as appropriate.