Aim of the study

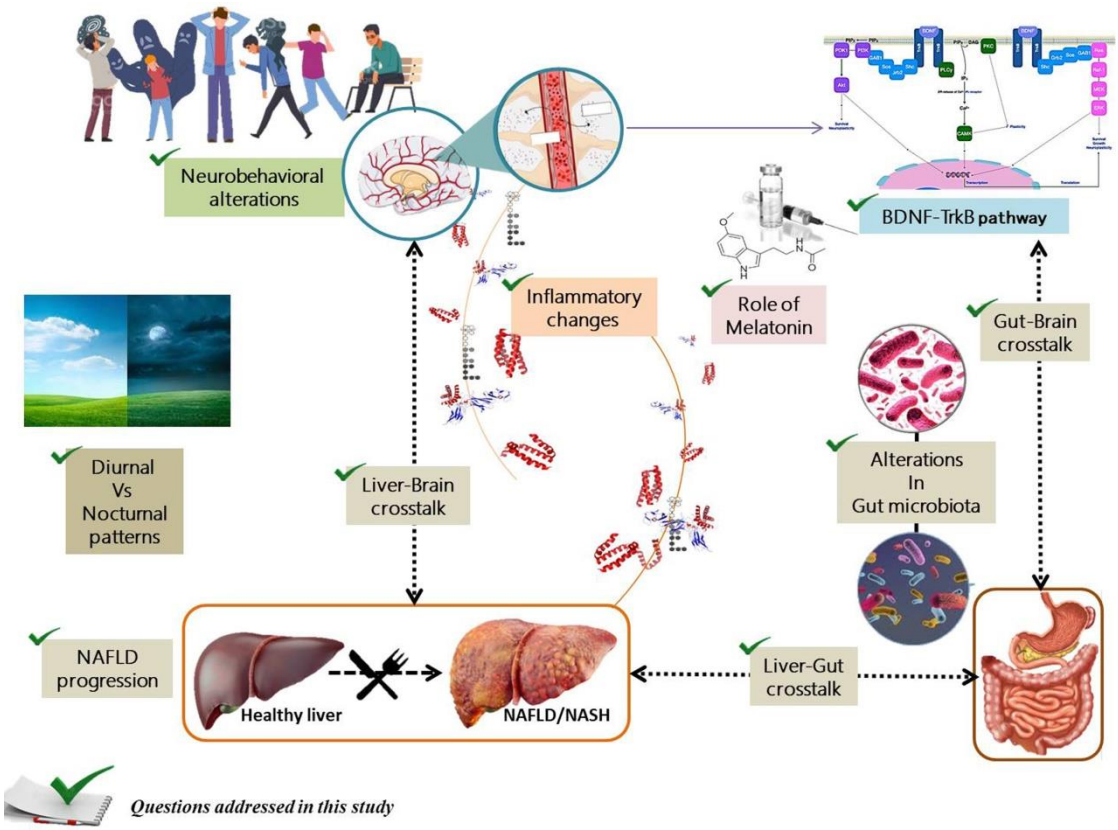
The aim of the study was to assess the NAFLD/NASH mediated neurobehavioral perturbations and subsequent corrective changes by exogenous melatonin treatment.

Objective 1	Correlating NAFLD/NASH mediated pro-inflammatory changes and alterations in gut microflora with neuro-behavioural shifts
Objective 2	Assessing melatonin mediated corrective changes in gut microflora and behaviour in said experimental models

Study outline

Experimentally induced circadian desynchrony (CD) and nonalcoholic steatohepatitis (NASH) was induced in C57BL/6J mice. Inflammatory changes in liver and brain were assessed followed by changes in the composition of Gut microbiota. A comparative account of diurnal and nocturnal behavioral shifts in CD and NASH mice were also studied using a variety of behavioural tests and quantified using AnyMaze software. These experiments were challenged with melatonin treatment and possible improvements in said parameters were assessed. Conclusive evidence on hepatic-hippocampal crosstalk in chronodisruption and nonalcoholic steatohepatitis was obtained by studying hippocampal BDNF-TrKb pathway.

Hypothesis


Neurobehavioral alterations
BDNF-TrkB pathway
Inflammatory changes
Role of Melatonin
Gut-Brain crosstalk
Diurnal Vs Nocturnal patterns
Liver-Brain crosstalk
Alterations In Gut microbiota
NAFLD progression
Healthy liver
NAFLD/NASH
Liver-Gut crosstalk
Questions addressed in this study

Thesis Chapters

The objectives were achieved and the entire study was divided into 5 chapters for clarity and better understanding.

1. ***Validation of experimentally induced circadian desynchrony (CD) and nonalcoholic steatohepatitis (NASH) in C57BL/6J mice***

   C57BL/6J mice were subjected to photoperiodic manipulation induced chronodisruption and/or high fat-high fructose diet induced non-alcoholic steatohepatitis was validated herein.

2. ***Inflammatory changes in liver and brain in experimentally induced Chronodisruption and/or Nonalcoholic steatohepatitis in C57BL/6J mice***

   Pro- and anti-inflammatory cytokines were assessed in serum, liver and hippocampal tissue, also the serum corticosterone rhythmicity was studied of experimental mice. Role of exogenous melatonin in improving hepatic-hippocampal inflammatory status and stress levels were studied herein.

3. ***Melatonin improves the composition of Gut microbiota in C57BL/6J mice fed with high fat-high fructose diet and/or subjected to chronodisruption***

   Alterations in the gut microbiota (faecal bacterial community abundance and diversity of the microbe composition) and its correlations with the disease pathology in experimental mice were studied. The merits of daily evening intraperitoneal administration of melatonin (10 mg/kg B.W) in preventing the disease induced alterations in gut microbiota are also studied.

4. ***Comparative account of diurnal and nocturnal behavioral alterations in CD and NASH***

   Shifts in neuro-behavioral traits were assessed using different neuro-behavioral test such as force swim and tail suspension for depression, hole-board, marble burying and elevated plus maze test for anxiety, morris water maze test for spatial learning and memory and locomotor deficits were evaluated using infrared actimeter in experimental mice subjected to high fat-high fructose diet and/or

chronodisruption. Role of exogenous melatonin in improving the diurnal/nocturnal neuro-behavioral alterations were studied herein.

5. ***Evidence on hepatic-hippocampal crosstalk in chronodisruption and nonalcoholic steatohepatitis***

   In the above mentioned experimental protocol, the objective was focused on the hippocampal BDNF-TrkB pathway and also the altered neurotrophic factors and its correlation with the previous objective such as hepatic-hippocampal inflammation status, altered gut microbiota and neurobehavioral perturbations. Also the corrective role of exogenous melatonin in improving hippocampal BDNF-TrkB pathway was studied herein.