P.019 The use of light to potentiate antidepressant medication: preclinical evidence

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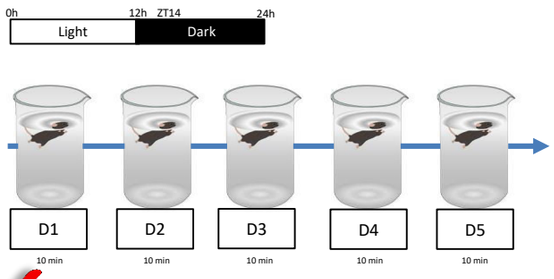
INTRODUCTION

Light was shown to synchronize the circadian clock and to modulate brain structures involved in sleep regulation, mood and cognition via specialized light sensitive melanopsin retinal ganglion cells (ipRGCs). Recently, an increased awareness of the effect of light on mood has been highlighted. Aberrant light cycles and/or disrupted circadian rhythmicity are known to produce depressive states and to impair cognition [1]. Inversely, light therapy has been shown to be effective in several forms of depression (seasonal, unipolar and bipolar depression). However, the underlying mechanisms through which light affects brain structures are still unknown. Recent studies emphasize that i) circadian and 5-HT systems are two important interactive regulatory brain networks that regulate mental health and ii) ipRGCs play an important role in mood regulation induced by light [2].

Hence, the purpose of our study is to decipher the neurobiological mechanisms by which light potentiates the antidepressant response, using an original model of depression [3].

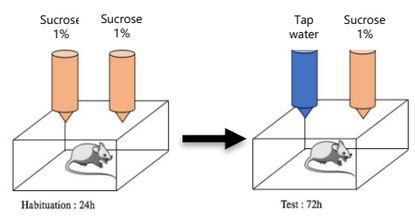
EXPERIMENTAL PROCEDURES

5 days Repeated Forced Swim Stress (5d-RFSS)



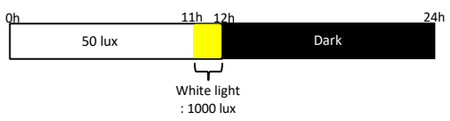
2 hours after lights off (ZT14), mice were put in a tank filled with water (25°C) and forced to swim 10 minutes daily for 5 consecutive days. The immobility time of the first 4 minutes of the stress was analyzed. Then, every week, a forced swim test was realized to follow the evolution of the behavioral despair.

Sucrose preference test



Mice were habituated to 2 bottles of sucrose (1%) during 24 h. Then, they were given the choice to drink from 2 bottles (1% sucrose solution and tap water bottle) during 72h. The positions of the bottles in the cage are switched every 24h to avoid possible side-preference effects.

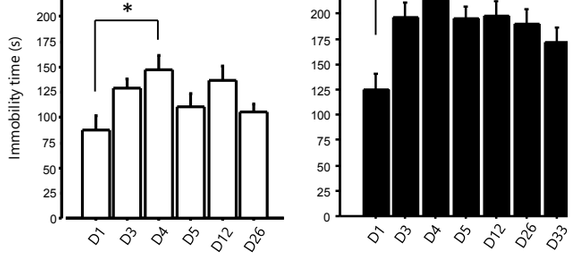
Light stimulation



At the end of the 5-dRFSS, mice were exposed everyday, for one hour (before the lights off), to a bright white light (1000 lux). The effect of light exposure on depressive-like behavior was analysed every week during 4 weeks post repeated stress.

An original model of depression

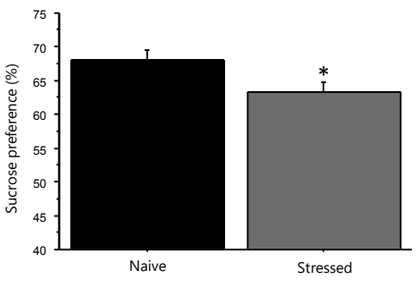
- Timing must be taken into account when using model of depression



6 week old C57BL/6 mice were forced to swim on 5 successive days (D) for 10 minutes at ZT1 or ZT 14. Animals were then tested every week. These results show that a stress at ZT14 (active phase) but not at ZT1 (resting phase), is effective to induce depressive-like behavior. Thus timing of stress is important

**p<0,05 ***p<0,001 vs D1 n=6*

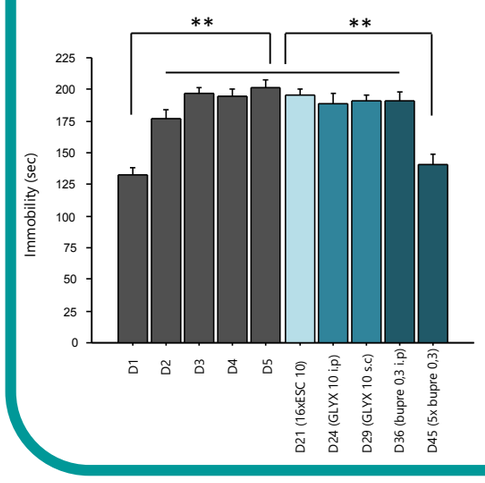
- Repeated forced swim stress induces anhedonia



Mice receiving the 5d-RFSS presented a sucrose preference reduced compared to naive mice, indicating that, in addition to behavioral despair, this stress caused anhedonia.

**p<0,05 following t-test. n=8*

- Model of treatment resistant depression

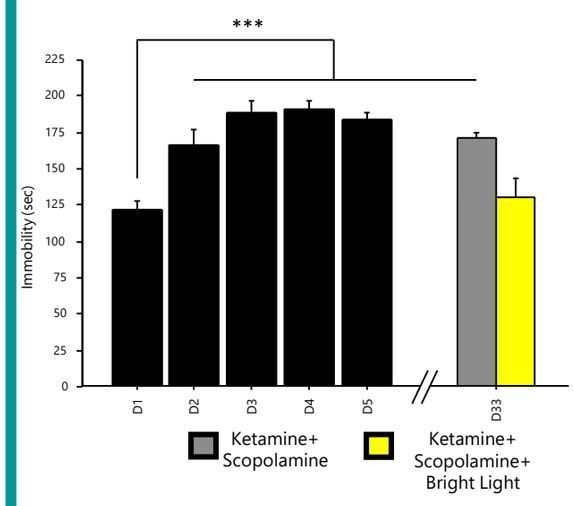


Neither a 2-week treatment with the SSRI escitalopram (10mg/kg, p.o.) nor a single injection of glyx-13 (10mg/kg, i.p or s.c), a NMDA modulator with glycine-like partial agonist properties, was able to reverse the behavioral despair induced by the 5d-RFSS. Interestingly, only a sub-chronic treatment with buprenorphine (0,3mg/kg, i.p.), a partial μ opioid receptor agonist and κ opioid receptor antagonist, was able to reverse this depressive-like behavior. These results emphasized 5d-RFSS as a novel model of treatment-resistant depression.

*** p<0,01 compared to D1 or D45 using repeated-ANOVA following Tukey-Kramer post hoc test. n=8*

Effect of bright light stimulation on behavioral despair

- Bright **light stimulation potentiates** the antidepressant response of a pharmacological treatment.



- The 5d-RFSS was sufficient to induce a stable behavioural despair over 4 weeks.
- A combination of sub-effective doses of the NMDA receptors antagonist **ketamine** (3mg/kg) + the muscarinic receptor antagonist **scopolamine** (0,1mg/kg) [4] failed to reverse the behavioural despair.
- However, a **4-week bright light** exposure (1h) added to the pharmacological combination of ketamine and scopolamine reduced the immobility time observed in the forced swimming test.

**** p<0,001 compared to D1 using One way repeated ANOVA followed by Tukey-Kramer post hoc test n=6*

- Serotonin is mediating the potentiating effect of bright light

3 injections of the tryptophan hydroxylase inhibitor **PCPA** (150 mg/kg) prevented the antidepressant effect of a combination of the NMDA receptor antagonist **ketamine** (3mg/kg) + the muscarinic receptor antagonist **scopolamine** (0,1 mg/kg) associated with **4 weeks of bright light exposure.**

**** p<0,001 compared to D1 using One way repeated ANOVA followed by Tukey-Kramer post hoc test n=6 to 9*

CONCLUSION

In this novel and validated model of depression, we show that the immobility time observed after 5 days of swim stress remain stable for more than 5 weeks and this mainly because the repeated stress is performed during the dark phase [5]. Repeated bright light exposure, for one hour/day during 4 weeks, potentiates the antidepressant effect of a sub-effective combination of ketamine and scopolamine. **This potentiation is mediated by the serotonergic system.**

Together, these results suggest, for the first time in a treatment-resistant model of depression, that light, in combination of a pharmacotherapy, can produce an antidepressant response. Studies are currently ongoing to determine the role of ipRGCs and the lateral habenula in this surprising antidepressant response.

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No potential conflict of interest. Poster presented at the 31st ECNP congress October 6th-9th, Barcelona Spain