

NMDA Receptor Antagonists Induce Antidepressant-like Sleep Changes: A Translational Model from Rats to Humans?

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Polysomnographic recordings enable the analysis of sleep behaviors and sleep pattern. Various classes of drugs exert common effects on sleep pattern: the vast majority of antidepressant drugs, for example, reduces Rapid Eye Movement (REM) sleep, whereas drugs that increase the cholinergic tone have the opposite effect. These observations have been used to translate effects of such medications across various species, from murines, cats, and dogs to healthy human volunteers and patients.

The anesthetic drug ketamine has recently been demonstrated to exhibit antidepressant-like effects in treatment-resistant major depressive disorder (e.g. [1,2]) and bipolar depression [3]. Antidepressant-like ketamine effects in animal models of antidepressant efficacy seem to correspond to these observations in humans (e.g. [4,5]). In this context we investigated whether antidepressant-like effects can also be observed in rat polysomnographic studies, as such studies are considered to be robust predictors of antidepressant effects in humans.

All experiments were conducted in accordance with the recommendations and policies of the National Institutes of Health Guide for the Care and Use of Laboratory Animals (1996 edition) and all applicable German laws and were approved by the respective Ethic Committee and Animal Welfare Offices. They were conducted in facilities with full Association for Assessment and Accreditation of Laboratory Animal Care accreditation.

Test compounds were administered to male Fisher rats chronically implanted with supracortical EEG electrodes. After dosing animals were transferred into individual cages inside a sound shielded box. Animals were randomly divided into 2 groups and tested in a crossover study design. At the first recording day they received either test compound or vehicle (sc), subsequently sleep EEG was recorded for 8h. After 7 days EEG was recorded a second time after receiving the alternative treatment (e.g. day 1 = test compound, day 8 = vehicle, or vice versa). All EEG recordings and analysis were performed with Sagura-Polygraph V2.0 (Dr. Cüppers Computer and Medizintechnik, Kelkheim, Germany). Analysis of sleep stages was performed in an automated manner and subsequently controlled by an experienced experimenter. For further polysomnographic analysis the following stages and patterns were differentiated: wake time, sleep I time (mild sleep), sleep II time (deep sleep including e.g. sleep spindles), REM time, number of REM episodes, latency to sleep and latency to REM.

Ketamine (3 - 30 mg/kg s.c.) significantly affected REM sleep parameters in an antidepressant-like manner (see Figure 1) similar to commonly used antidepressants (inhibitors of serotonin reuptake, tricyclics, and inhibitors of the monoamine oxidase). The number of REM episodes, and the total REM time were significantly decreased; likewise, latency to first REM was increased. These effects are mechanism-related as they were reproduced with the NMDA antagonist MK-801.

The above results clearly demonstrate an antidepressant-like profile of ketamine in rat polysomnographic studies consistent with efficacious doses found in other antidepressant models [6]. These results are in line with the clinical antidepressant effect of ketamine therapy.

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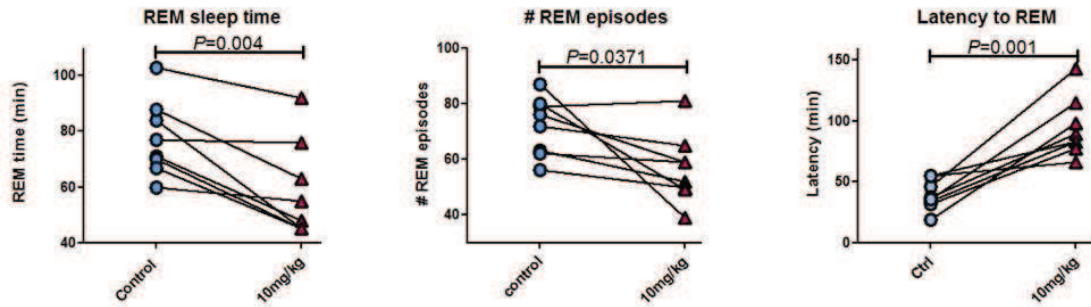


Figure 1. Ketamine (here at 10 mg/kg, ip) significantly affects REM sleep parameters in an antidepressant-like manner. The number of i) REM episodes and ii) the total REM time were significantly decreased; iii) latency to first REM was increased. (paired t-test, see P-values in figures)

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