A study of a topiramate pre-treatment on the effects induced by a subanaesthetic dose of ketamine on human reaction time

Joëlle Micallef a, Gilles Gavaudan a, Boris Burle b, Olivier Blin a, Thierry Hasbroucq b,c,∗

a Centre National de la Recherche Scientifique et Université de la Méditerranée, Institut des Neurosciences Cognitives de la Méditerranée, Assistance Publique Hôpitaux de Marseille, France
b Centre National de la Recherche Scientifique et Université de Provence, Laboratoire de Neurobiologie de la Cognition, 31 Chemin Joseph-Aiguier, 13402 Marseille, Cedex 20, France
c Institut de Médecine Navale du Service de Santé des Armées, Toulon, France

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Abstract

Ketamine, a N-methyl-d-aspartate (NMDA) receptor antagonist, impairs reaction time performance and interacts with foreperiod duration, thereby suggesting that ketamine alters motor preparation. These effects can be attributed either to the blockade of NMDA receptors or to the stimulation of α-amino-3-hydroxy-5-methylisoxasole-4-propionic acid (AMPA) and kainate receptors. The purpose of the present study was: (i) to replicate previous findings and (ii) to study the effect of a pre-treatment with topiramate, an AMPA/kainate antagonist, on the impairments induced by ketamine on RT. Thirty six healthy subjects (3 groups of 12) performed a two-choice RT task in which the foreperiod was manipulated. All subjects performed the task under perfusion of ketamine (intravenous bolus of 0.12 mg followed by a perfusion of 0.5 mg/kg over 60 mn) or placebo (saline). Depending on the group, an oral dose of topiramate (50 mg) or placebo (lactose) was administered 2h before ketamine infusion (randomised, double-blind, double-dummy, parallel-group design). At the dose studied, topiramate exerted no detectable effect on RT. The results relative to ketamine corroborate previous findings and suggest that this molecule affects motor preparation through the blockade of NMDA receptors.

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We recently investigated the effect of a subanaesthetic dose of ketamine, a non-competitive N-methyl-d-aspartate (NMDA) receptor antagonist, on human information processing [10,17]. During perfusion of a subanaesthetic dose of ketamine or a placebo, the subjects performed a two-choice visual reaction time (RT) task in which the foreperiod, that is the interval separating a warning signal from the response signal, was manipulated. Reaction time was longer under ketamine than under placebo and for a two-second-and-a-half foreperiod than for a half-second foreperiod. Furthermore, the latter effect, that corroborates innumerable previous behavioural results [3,11,19], was markedly enhanced under perfusion of ketamine. This enhancement of the foreperiod effect suggests that ketamine impairs motor processes [22,23]. Moreover, this effect was independent of the level of vigilance as suggested by the lack of correlation between RT performance and vigilance state as assessed by visual analog scales [17]. Since, to the best of our knowledge, this work constitutes the unique report of an effect of ketamine on human RT and that it has been conducted in a small sample of subjects (∗N = 8), the first aim of the present study was to replicate our previous findings.

The second aim was to investigate the mechanisms by which ketamine impairs human RT performance. On the basis of our previous results, we proposed that NMDA receptors play a critical role in motor processes [19]. This interpretation, however, can be challenged because it has been suggested that NMDA receptor antagonists may induce two opposite effects on glutamatergic neurotransmis-
sion. Indeed, ketamine entails a primary postsynaptic reduction of glutamatergic neurotransmission at the NMDA receptors and a secondary increase in glutamatergic transmission at \(\alpha\)-amino-3-hydroxy-5-methylisoxasole-4-propionic acid (AMPA) and kainate receptors \[1,12,13,18\]. One way of deciphering which of these alternatives better accounts for the functional effects of NMDA antagonists consists in studying the effect of a treatment with AMPA/kainate antagonists on the ketamine-induced deficits. It has been demonstrated, in animal models \[4,18\], that the administration of AMPA/kainate antagonists (topiramate and CNQX or LY293558, respectively) can reduce behavioural effects of NMDA antagonists (MK 801 and ketamine), which indicates that the neurotransmission at AMPA/kainate receptors is involved in these effects. In humans, lamotrigine was shown to be markedly superior to placebo in reducing the deficits induced by ketamine, leading Anand et al. \[1\] to conclude that lamotrigine attenuates ketamine effects by inhibiting glutamate release at non-NMDA receptors.

In the present study, we evaluated the effect of a pre-treatment with topiramate, an AMPA/kainate receptor antagonist, on the RT of healthy subjects under perfusion of a subanaesthetic dose of ketamine. The subjects’ task was similar to that used in our previous study and the duration of the foreperiod was manipulated. In the event of a reduction in glutamatergic neurotransmission due to NMDA receptors blockade, the effect of ketamine on RT was expected to be unaffected by the topiramate absorbed as a pre-treatment. In contrast, in the event of an increase in glutamatergic neurotransmission at AMPA/kainate receptors, the effect of ketamine on RT was expected to be reduced by the pre-treatment. Note, however, that, while the verification of these predictions would provide evidence relative to the joint effects of ketamine and topiramate, they would not be unequivocal, because the latter molecule has several modes of action (blockade of voltage-dependent sodium channels, potentiation of GABAergic transmission, inhibition of carbonic anhydrase and inhibition of excitatory pathways through AMPA/kainate receptor sites \[20\]).

Thirty six males volunteers, aged 20–35 (mean = 26) were initially recruited for the study and received an indemnity for their participation in the study as outpatients. All the subjects had body weights within predefined limits for their height (their weight did not exceed 10% of the ideal weight as defined by the tables of the Metropolitan Life Insurance). Before the study began, health was established by means of medical and psychiatric history, physical examination, electrocardiogram and blood tests (serum biochemistry and haematology). None of the subjects had used psychoactive drugs within the last four weeks and none was currently taking any prescription drugs. Urinary tests were performed to discard individuals taking psychoactive drugs (barbiturates, benzodiazepines, cannabinoids, cocaine, opioids). Heavy smokers were discarded from the study: all the subjects were non-smokers or smoked less than ten cigarettes a day and were able to abstain from smoking on the testing day. Their visual acuity was normal. The subject’s mental state was judged satisfactory on the basis of the DSM IV and of an interview performed by a psychiatrist. Alcohol and caffeine consumption were prohibited during the 24 h preceding the tests and during the test day. The protocol received the approval of the local ethics committee (CCPRB Marseille 1), and the subjects gave their informed written consent according to the declaration of Helsinki.

The topiramate pre-treatment, was a single 50 mg dose of a clinically available agent, Epitomax\(^\text{®}\), which is indicated as an adjunctive therapy for patients with partial-onset seizures or primary generalised tonic-clonic seizures. The Summary of Product Characteristics recommends a starting dose of topiramate 25–50 mg/day in patients, explaining the choice of a single 50 mg dose in the present study. Previous studies using higher doses (400, 200, 100 mg) induce unacceptable central nervous system reactions in non-epileptic subjects \[16\]. In the present study, these adverse events could be potentiated by ketamine. In particular, sedative effects may impair task performance \[15\].

Clinical pharmacokinetic studies have shown that a mean peak plasma concentration \(C_{\text{max}}\) of 1.5 mcg/ml of topiramate is achieved within 2–3h after oral absorption and the half-life of this molecule is 20–30h \[20\]. The mode of action of topiramate is multifactorial and involves the blockade of voltage-dependent sodium channels, potentiation of GABAergic transmission, inhibition of carbonic anhydrase and inhibition of excitatory pathways through AMPA/kainate receptor sites \[20\]. This pre-treatment and its placebo (lactose) were supplied as indiscernible capsules. Ketamine hydrochloride (Ketalar\(^\text{®}\) ) and its placebo (saline) was administered as an intravenous bolus of 0.12 mg/kg over 1 min, followed by a constant intravenous perfusion of 0.5 mg/kg over 60 min. The dose used in the present study was selected on the basis of our previous study that showed that it affects RT but is subanaesthetic \[10,17\]. In order to maintain the double-blind, the placebo (saline) was similarly administered.

The subject sat at a table, facing a row of three light-emitting diodes (LEDs) disposed slightly below the line of gaze. Two response keys were fixed lateral to the body midline, 30 cm apart. The central LED—permanently off—served as fixation, the two outer LEDs as imperative stimuli. A chin rest was used to maintain the subject’s eyes 50 cm away from the central LED. The distance between the two outer LEDs and the central one subtended 7° of visual angle. A locally built sound generator was used for presenting the warning signal.

The experiment took place in a dimly lit room. A trial began with the onset of a warning signal (2500 Hz, 75 dB, 50 ms): 500 ms (short foreperiod) or 2500 ms (long foreperiod) later, a lateral LED was lit (variable intensity, 2.5 mcd on average). The response, a press on one of the two keys, extinguished the stimulus. The left and right keys were to be pressed with the left and right index, respectively.

The study was a randomized, double-blind, double-dummy, parallel group design. Each subject was randomly as-
signed to one of three groups of twelve, each group receiving a different combination of pharmacological treatment. The subjects of group 1, thereafter termed "Top/Plc", absorbed a topiramate capsule as a pre-treatment and were perfused with the placebo (saline); the subjects of group 2, thereafter termed "Plc/Ket", absorbed a placebo capsule as a pre-treatment and were perfused with ketamine; the subjects of group 3, thereafter termed "Top/Ket", absorbed a topiramate capsule as a pre-treatment and were perfused with ketamine.

Trials were presented in blocks of 68. The first four trials were warming-up trials. Within a block, each of the possible stimuli (to the left or to the right of the point of fixation) whose strong or weak luminance was unpredictable (see [10]) lit up equally often according to a random sequence.

The subjects came twice to the hospital. The two visits were spaced out by a maximum of 20 days. The first visit, was meant to allow the selection of the subjects for inclusion in the study (see above) and served to train the selected subjects to the task. The second visit was devoted to the experiment. The subjects were to perform one training session during their first visit and two experimental sessions during the second one. During each of these sessions, the subjects performed successively one block of trials with the short foreperiod and one block with the long foreperiod. Foreperiod was therefore blocked; the order according to which the two types of blocks were completed was balanced across subjects. A few minutes of rest were given between each block of trials. Overall a session lasted about 15 min.

For their second visit, the selected subjects were admitted at the hospital at 08:00 h and slept in the hospital. The following day, they performed a first experimental session at 08:00 h. The perfusion (ketamine or saline) was installed at 11:00 h and removed at 12:00 h. The topiramate or placebo was administered 2 h before ketamine, on the basis of the time of the peak of the topiramate blood-level. At 11:30 h, the subjects were to fulfil visual analog scales designed to assess complementary aspect of sedation by allowing the subjects to rank themselves as more or less tired, drowsy, woosy, clumsy, fine and energetic. The second experimental session was performed at 11:40 h. The subjects remained under medical monitoring the next 8 h following the removal of the perfusion.

Because of drowsiness and nausea (vomiting, orthostatic hypotension), two subjects, one in the Plc/Ket group and one in the Top/Ket group, could not complete the second experimental session. Their data and those of a third subject of the Top/Ket group, who could not complete the experiment because of an electronic malfunction, were discarded from the analyses. The number of subjects, was therefore 10, 12 and 11 in the Top/Ket, Top/Plc and Plc/Ket group, respectively. At baseline, the three groups were found to be equivalent as regards to age, weight and RT performance.

Errors (incorrect overt responses) occurred in 0.67% of the trials and were judged too scarce for an analysis. The RTs were summarized by individual means per condition. These untransformed data were submitted to different analyses of variance with foreperiod duration and/or session as within-subject variables. The first session corresponds to the blocks of trials performed before the administration of any pharmacological treatment. The second session corresponds to the blocks of trials performed after oral absorption of topiramate or placebo and under perfusion of ketamine or placebo. The effect of session thus reflects both the effect of practice and the effect of the medications that differed across groups of subject. The results are presented in Fig. 1.

First, in order to estimate possible between-group differences, we analysed on their own the data collected during the first session. The analysis of variance involved one between-subject variable, the group, and one within-subject variable, the duration of the foreperiod. The subjects displayed shorter RTs for the short (274 ms) than for the long foreperiod (285 ms, F(1,30) = 29.09, P < 0.01). There was no effect of group, neither as a main effect nor as a component term in its interaction with foreperiod duration (all F's < 1). These results replicate the effect of foreperiod on RT and indicates that, prior to the administration of any medication, the groups were not different in terms of RT (see Fig. 1).

Second, three separate analyses of variance were performed on the respective data of three groups of subjects. Each of them involved foreperiod duration and session as within-subject variables. In the Top/Plc group, the subjects reacted faster for the short (268 ms) than for the long (286 ms) foreperiod (F(1,11) = 15.13, P < 0.01). Session exerted no detectable effect on RT (F(1,11) < 1). There was no hint of interaction between foreperiod duration and session (F(1,11) < 1). In other words, these results confirm that foreperiod duration affects RT and suggest that neither practice nor topiramate in isolation affect the subjects’ performance (see Fig. 1).

In the Plc/Ket group, the subjects reacted faster for the short (298 ms) than for the long (316 ms) foreperiod (F(1,10) = 9.64, P < 0.025) and during the first (277 ms) than during the second session (327 ms, F(1,10) = 15.22, P < 0.01). The effect of foreperiod duration was larger during the second (46 ms) than during the first session (10 ms, F(1,10) = 7.09, P < 0.05). Since practice decreases rather than increases RT
Hasbroucq et al. [11] presented evidence that the foreperiod can influence the excitability of corticospinal structures. The duration of the foreperiod is increased. Electrophysiological studies have accumulated evidence that foreperiod duration influences the recruitment rate of the motor units, the recruitment being more phasic for short than for longer foreperiods. The present results show that the effect of foreperiod is larger under ketamine that under placebo, which confirms that the glutamnergic system is involved in motor preparation. Furthermore, since our previous study suggested that ketamine interacts with foreperiod duration but not with other factors affecting sensory and central processes, one may tentatively conclude that it is specifically involved in motor processing [10].

As stressed above, the interpretation of the neuropharmacological effects of ketamine cannot be straightforward because they can result from opposite effects on glutamnergic neurotransmission. Most cortical excitatory projections being glutamnergic, a first possibility is that ketamine disrupts the cortico-striato-thalamo-cortical interactions through NMDA receptors. A second, alternative possibility is that ketamine stimulates glutamate release through AMPA/kainate receptors. In order to evaluate these alternative hypotheses, we studied the influence of a pre-treatment of topiramate, an AMPA/kainate receptor antagonist, on the effects induced by ketamine on RT. The main effect of ketamine on RT as well as its interaction with the foreperiod duration remained unchanged under topiramate.

It is of course possible that the dose of topiramate employed was insufficient to have a pharmacodynamic effect. Two observations, however, contradict this interpretation. First, several subjects of the Top/Plc group presented central nervous system adverse effects (headache, limb paresthesia, dizziness, drowsiness), some of which are typical topiramate side-effects. Second, in another study, we have shown that the same single 50 mg dose of topiramate attenuated the effect of ketamine in an anti-saccade task [5]. These observations are in favour of a pharmacodynamic effect of topiramate at the dose used in the present study. It must, however, be acknowledged that in the present study, the potential sedative effects of topiramate could prevent the potential manifestation of other effects on information processing. Note, however, that in the Top/Plc group the lack of correlation between the effect of ketamine and the visual analog sedation scales could be assessed with the spearman correlation test (the $r$ values being $-0.087$, $-0.52$, $0.2263$, $0.3101$, $0.4266$ and $0.0325$ for tiredness, drowsiness, wooziness, clumsiness fitness and energetic feeling, respectively).

The present results first replicate those of our previous study showing that ketamine impairs the subjects’ performance and interacts on RT with the effect of foreperiod duration [10,17]. The effect of foreperiod duration is generally ascribed to motor preparation strategies [19,24]. In order to comply with the task instructions, the subjects attempt to synchronize their readiness to the onset of the response signal. Because motor preparation can be optimal for only a few tens of milliseconds [9], it is set according to the subjects’ expectations concerning the occurrence of the response signal. Since the absolute accuracy of the time estimation decreases as the duration to be estimated increases [8], the subjects’ preparation is better timed for short foreperiods than for longer ones (for a review, see [21]). As a consequence, RT lengthens as the duration of the foreperiod is increased. Electrophysiological studies have accumulated evidence that foreperiod duration can influence the excitability of corticospinal structures. Hasbroucq et al. [11] presented evidence that the foreperiod
neurogenic disorders and that this disease is associated with movement disorders often hyperkinesias and less frequently, bradykinesia and akinsia [2].

The above interpretation, however, is only tentative because of the multiple effects of topiramate. Indeed, topiramate antagonizes AMPA/kainate receptors, but also blocks voltage-dependent sodium channels, potentiates GABAergic transmission, and inhibits carbonic anhydrase and excitatory pathways through AMPA/kainate receptor sites [20]. Future studies addressing the functional effect of ketamine should, therefore, investigate the action of molecules more specific to AMPA/kainate receptors.

References