The role of Ketamine in treatment-resistant Obsessive Compulsive Disorder (OCD)

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•Background

Obsessive-compulsive disorder (OCD) is a relatively common and frequently debilitating neuropsychiatric disorder that affects approximately 1–3% of the general population; it is characterized by recurrent persistent thoughts (obsessions) and repetitive compulsory behaviours (compulsions).

The selective serotonin reuptake inhibitors (**SSRIs**) are the mainstay of pharmacotherapy and are of benefit in the majority of patients, but as many as 10–20% of patients fail to improve.

Even if OCD aetiology has not been fully elucidated, there is growing evidence that **glutamate signalling dysfunction in the CSTC** (cortico-striatal-thalamo-cortical) circuitry plays a role in its pathogenesis **[1] .**

Ketamine, a **NMDA receptor antagonist**, is a **glutamatergic modulator** and its s-enantiomer, Esketamine, has been used and approved by the FDA and EMA for treatment-resistant depression (TRD).

This brief review aims to define whether this molecule could also be used to treat resistant-OCD.

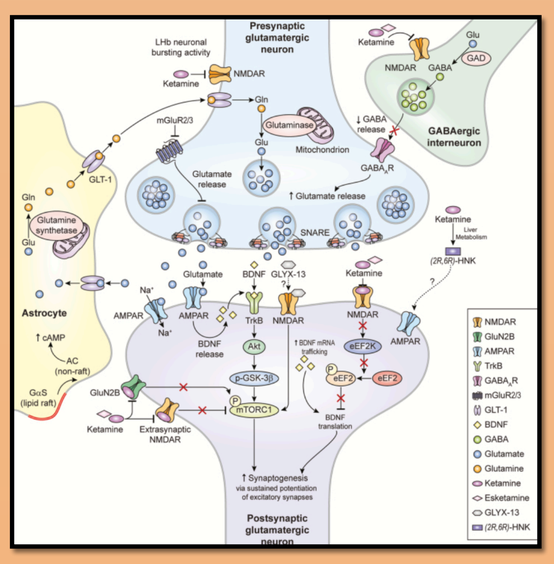

Fig. 1 Mechanism of action of Ketamine [2]

The effect of Ketamine can be explained by a multitude of signalling pathways (**Fig. 1**), involving the **blockade of NMDA** receptors both expressed on **glutamatergic neurons** and **GABAergic interneurons [2].**

The antagonism of NDMA on post-synaptic glutamatergic neurons reduces the phosphorylation and activation of eukaryotic elongation factor 2 (**eEF2**) which is involved in the release of **BDNF** in the neuronal ambient.

In addition, it has been shown that in the PFC (prefrontal-cortex) Ketamine preferentially blocks NMDARs present on GABAergic interneurons, which, in turn, increases the firing of pyramidal neurons with a consequent **glutamate burst.**

This glutamate burst increases AMPAR-mediated excitatory transmission, which, in turn, increases the release of **BDNF at synapses** and **activates mTOR [3].**

The release of **BDNF** in the synaptic area and its positive effect on **mTORC1** pathway lead to **synaptogenesis** and promotes **neuronal plasticity (Fig.2).** This molecular mechanism is considered to have a role in decreasing depressive and compulsory symptoms.

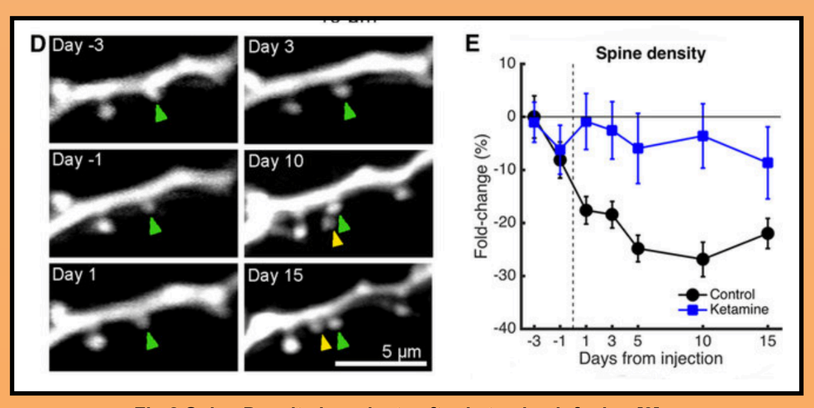

Fig.2 Spine Density in rodents after ketamine infusion [3]

•Methods

The literature regarding this topic is still at its dawn. The bibliographic research was conducted on a time interval of 10 years (2010-2020) using PubMed, SCOPUS and Google Scholar as database and: “Ketamine”,“OCD”, “obsessive compulsive disorder”, “obsessions”, “compulsions” “mice”, “Marble Burying Test”, “Esketamine”, “glutamatergic system”, as keywords.

•Results

Most of the studies on animal models tried to mirror OCD symptoms and phenotypes with different techniques such as genetic, pharmacology and behavioural.

One of the behavioural tests that is considered to be reliable in mimicking OCD-like symptoms is the Marble Burying Test. The test is based on a repetitive digging of some objects present in the cage.

In the study performed by *Cristiana Luz Tosta et al* **[4]**, the mice that were treated with a **single systemic administration of S-ketamine** (10,20mg/kg) had a **significant reduction of buried marbles**, compared to the controls ($p < 0.05$); while S-ketamine 3 mg/kg had no effect ($p > 0.05$) **(Fig. 3)**. Moreover, the distance travelled during the test proves a connection between stress and motor activity ($P < 0.05$). **(Table 1).** The study included a positive control that received fluoxetine (SSRI), which is used to treat OCD.

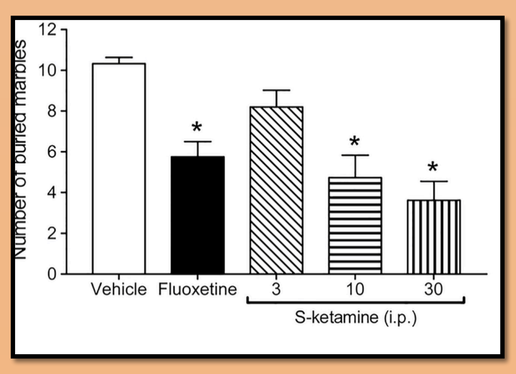

Fig. 3 Number of objects buried depending on Ketamine administration [4]

Treatment	N	Total Distance travelled (m)[a]	Number of entries in the central area [a]	Distance travelled in the central area (m) [a]
Vehicle	15	23.01 ± 1.53	24.33 ± 2.15	4.46 ± 0.54
Fluoxetine 10 mg/kg	8	18.32 ± 1.17	21.50 ± 3.06	4.26 ± 0.63
S-ketamine 3 mg/kg	15	21.05 ± 1.69	20.70 ± 2.36	3.11 ± 043
S-ketamine 10 mg/kg	11	18.66 ± 1.52	24.20 ± 2.43	4.68 ± 0.23
S-ketamine 30 mg/kg	13	15.89 ± 1.29 *	15.38 ± 1.63 *	2.59 ± 10.26 *

Table 1, distance travelled during the test [4]

In the first study on humans **[5]**, an infusion of ketamine (0.5mg/kg over 40 minutes) was administered in 10 subjects with resistant-OCD, and pre and post-treatment evaluation was made by using YBOCS (Yale-Brown Obsessive-Compulsive Scale).

The efficiency of ketamine was significant but transient: it reduced the OCD symptoms at **1 hour from the infusion** (maximum reduction of 60% of the symptoms) but **did not seem to persist after the acute effect** has dissipated. Y-BOCS improvement was slight but statistically significant over days 1–3 following ketamine infusion (p=0.005). **(Fig. 4)**

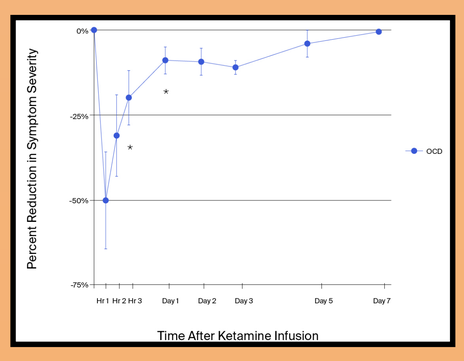

Fig. 4 Variation of OCD symptoms in time (Bloch et al, [5])

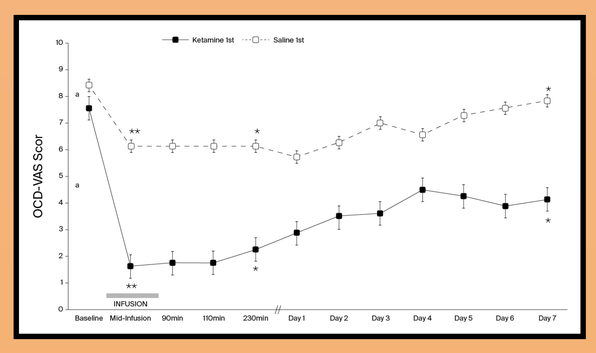

Fig. 5 Variation of OCD symptoms in Time (Rodriquez et al, [6].)

The second study **[6]** was a randomized and controlled one that included 15 participants divided into two groups.

The results highlighted that the group treated with Ketamine showed a **reduction of both OCD-behaviours and scales scores right after the administration** that, in contrast with the first study, **perisists for one week**. The control group (saline solution) did not show any variation in the scales scores.

Specifically, those receiving ketamine had lower OCD-VAS score (OCD visual analog scale) at mid-infusion (p<0.005), 230 min (p<0.005), and 7 days (p<0.005) post infusion, than those receiving placebo **(Fig. 5).**

•Discussion and Conclusion

In general, the use of Ketamine **showed a rapid and significant decrease of OCD symptoms both in humans and animals.**

Since the results are promising, the application of Ketamine in resistant-OCD **deserves to be further investigated** by new approaches (i.e. hIPCs disease modelling and other animal disease modelling) to fully understand the mechanisms of action.

Moreover, other human trials should be performed with larger samples of patients, repetitive administrations and long-term observation.

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