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WHAT DO ECT RTMS AND KETAMINE SHARE FOR TREATMENT REFRACTORY DEPRESSION

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ABSTRACT

This study reviews the common pathways of antidepressant action of electroconvulsive treatment (repetitive trans magnetic stimulation and ketamine which have distinguished themselves as potentially effective treatments for major depression. In general, traditional antidepressants-mono amine oxidase inhibitors, selective serotonin reuptake inhibitors and norepinephrine re update inhibitors - exert antidepressant influence by normalizing prefrontal cortex dopamine function over several weeks. Diverse and converging evidence suggests that ketamine, rTMS and ECT share common biological properties to induce anesthesia, analgesia, antidepressant effect and elevation of serum endorphins and these observations highlight the central importance of the endorphin-opioid system in normal brain function, mood and pain regulation. Furthermore, it seems that, their antidepressant effects may correspond to a triad of signature traits of anti-glutamatergic, dopaminergic. and opioid agonistic influences. rTMS and Ketamine enhance PFC metabolism and regional blood flow in contrast to ECT which shows negative or no effect on these functions. These intzimate associations involving glutamate opioid and dopamine pathways are worthy of emphasis especially in the context of the global connectivity and complexity of human brain function governed by the evolutionary predominant influence of prefrontal cortex.

KEYWORDS: Ketamine; ECT; rTMS, Opiates; Endorphines.

What do ECT rTMS and Ketamine Share for Treatment Refractory Depression?

Major depressive disorder is a highly prevalent illness associated with significant morbidity and mortality.[1,2] Diverse studies suggest despite the advances in the treatment of major depression up to 35% of patients fail to respond to drug therapy.[1,2] Also, it is estimated that approximately more than 40,000 people commit suicide every year in the United States.[3] In general, depressions that fail to respond to two or more different antidepressant drugs at adequate dosage and duration are defined as treatment refractory depression and they seem to have a significantly higher likelihood of not responding to another antidepressant.[1,2]

Among many therapeutic interventions for treatment refractory depression ECT (electroconvulsive treatment)[4] r-TMS (repetitive trans magnetic stimulation[5] and ketamine[6] have distinguished themselves as potentially effective treatments. However, their precise mechanism of action seems to be a topic of controversy.

In view of the complexity and global connectivity of brain function a single brain region or neurotransmitter cannot be the hypothetical cause of treatment refractory depression. However diverse biological markers associated with interconnected biological dysfunctions may offer novel insights into the underlying processes leading to depression.

The aim of this review is to investigate possible pathways of antidepressant action of TMS, ECT and ketamine for our knowledge may help future research directions to discover intelligent solutions for this debilitating brain disorder.

In this article, I will first review psychobiology of depression, then review antidepressant effects of ketamine and ECT and TMS and the mechanisms of action .Finally, I will conclude with a discussion of future areas for exploration.

Psychobiology of depression

Diverse animal studies, clinical and neuro imaging observations suggest most depressions represent complications of diverse brain dysfunctions that lead to abnormalities in dopamine system.[7,8] Noteworthy is the observation of neuroimaging evidence of prefrontal cortex dysfunction and regional blood flow and metabolism deficits in people with major depression.[9-12] In general, it has been observed that traditional antidepressants-mono amine oxidase inhibitors, selective

serotonin reuptake inhibitors and norepinephrine re update inhibitors - exert antidepressant influence by normalizing prefrontal cortex dopamine function over several weeks.[7,8] It has also been suggested that the therapeutic efficacy of antidepressant strategies may depend less on their presumptive molecular mechanisms of action and more on their ability to restore the predominant metabolic and executive functions of the prefrontal cortex and dampen excessive subcortical and limbic influences.[11]

In 1979, Brozoski and colleagues demonstrated the importance of dopamine depletion in prefrontal cortex as a major influence in depression.[13]

Depression like syndrome caused by depletion of dopamine in prefrontal cortex of rhesus monkey as severe as caused by the surgical ablation of the same area, can be pharmacologically reversed with dopamine agonists such as L-dopa and apomorphine.[13]

It is true that In brain function-a complex system- neither a single abnormal neurotransmitter nor a dysfunctional brain region can independently determine the nature or severity of a particular disorder such as depression. In essence any brain dysfunction corresponds to dynamic interactions of diverse and multiple influences.

Consistent with the connectivity and complexity of brain function, the final pathway for changes in mood seems to represent the prefrontal cortex dopamine function. In essence diverse pathways and regional brain dysfunctions may lead to depression by almost always contributing to a common denominator of abnormal prefrontal cortex dysfunction.

Electroconvulsive therapy (ECT)

ECT, has been an important treatment for severe and treatment-resistant depression dating back to the middle of the 20th Century.[5,7,8]

A wealth of preclinical and clinical data attest to ECT's potent antidepressant action. A meta-analytic review of randomized controlled trials that compared ECT with simulated ECT or placebo or antidepressant drugs and by a complementary meta-analytic review of nonrandomized controlled trials that compared ECT with antidepressants drugs revealed a significant superiority of ECT in all comparisons: ECT versus simulated ECT, ECT versus placebo, ECT versus antidepressants in general, ECT versus TCAs and ECT versus MAOIs.[14] The nonrandomized controlled trials also revealed a significant statistical difference in favor of ECT when confronted with antidepressants drugs.[14-18]

ECT seems to enhance dopaminergic, serotonergic, and adrenergic neurotransmission.[19,20] There's also evidence ECT alters GABA and glutamate systems.[21,22]

ECT seems to promote a release of hypothalamic or pituitary hormones, including endorphins.[23,24] Animal studies have demonstrated increased neurogenesis and synaptogenesis within the rat hippocampus after electroconvulsive shock (ECS), in an animal model of ECT.[25,26]

Neurotrophic factors, such as brain-derived neurotrophic factor, have been shown to be increased after ECT in humans.[27]

Surprisingly, observation from the neuroimaging studies of ECT do not show any changes in the hypofrontalism associated with major depressions.[28,29,30] Nobler and colleagues reported that a course of bilateral ECT reduced regional cerebral metabolic rate for glucose in medication-free patients with major depression.[28] These decreases were widespread and most significant in the frontal, prefrontal, and parietal cortexes. Further, both statistical parametric mapping and region-of-interest analyses were consistent in identifying metabolic reductions.[28]

The endorphin response to electroconvulsive therapy (ECT) has been demonstrated. A study of 10 patients showed a significant rise of plasma endorphin levels after ECT.

This increase returned to the pre-ECT level within 1 hr after ECT.[31] Similar findings were also reported by another study.[32] Possibly consistent with the enhancement of endorphins it has also been shown that ECT may have analgesic properties demonstrated by case reports and studies.

Interestingly the first case report of pain relief from ECT dates back to 1949 when Bornstein described three patients who had suffered from phantom limb phenomenon and became pain-free after ECT treatment.[33] Pisetsky described a 55-year-old man status post bilateral below- knee amputations with painful phantom limb discomfort. There was complete resolution of the phantom limb sensations along with the depression after ECT.[34]

King and Nuss reported a patient with reflex sympathetic dystrophy treated successfully by electroconvulsive therapy.[35] Also, positive response to ECT was observed by Mc Daniel in three patients with complex regional pain syndrome.[36]

A case-matching study comparing outcomes of inpatients with chronic pain and major depression treated with ECT and medications indicated that ECT had analgesic properties independent of its improvement of depression. Improvements in depression were similar, while there was a significantly greater improvement in pain with ECT. The lower post-ECT treatment pain scores suggested a specific analgesic effect of ECT.[37]

Based upon a comprehensive literature review Rassmussen and Rommans concluded that some sub group of patients with chronic pain may benefit from ECT.[38]

There have been two studies demonstrating no observable improvement following ECT treatment in patients with central pain or fibromyalgia.[39,40]

Salmon and colleagues conducted an open label study of four patients with intractable thalamic pain and found no significant change in pain.[39]

The effect of ECT on depression and other symptoms of fibromyalgia was studied in a prospective 3-month trial in 13 patients with fibromyalgia and concomitant depression. The study results indicated observable benefits for mood but no improvement in pain.[40]

In summary ECT may have antidepressant and analgesic properties, increases serum endorphins, enhances dopaminergic, serotonergic and opioid transmission.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Several prospective, double blind studies suggest that (rTMS) may be effective for both major depression and treatment refractory depression.[41-45] Also, several independent reviews and meta-analysis suggested that rTMS had antidepressant properties.[46,47,48,49]

It has been observed that rTMS modifies human pain perception and seems to have opposite effects when applied over the sensory motor cortex and medial frontal cortex:. rTMS over sensory motor cortex can enhance whereas over medial frontal cortex suppresses central processing of pain perception.[50]

A study by Johnson and colleagues indicated that high frequency TMS increased the sensory threshold of pain in patients suffering from chronic pain.[51]

In a study of 48 patients with therapy resistant chronic unilateral pain syndromes (with trigeminal neuralgia and post-stroke pain syndrome) five daily sessions of rTMS over motor cortex produced long lasting pain relief.[52] Also, eighteen patients with intractable neurogenic pain experienced transient pain relief by 10 Hz rTMS of the motor cortex.[53]

In addition, independent studies confirm that rTMS over motor cortex can produce long lasting pain relief in patients with phantom pain and also elevates serum beta-endorphin concentration.[54,55] The role of β endorphin in pain relief following high rate repetitive transcranial magnetic stimulation in migraine has also been demonstrated.[56] 93 patients having more than four migraine attacks per month received 10 Hz rTMS to left motor cortex and were compared to 47 patients who received sham stimulation. The study results indicated that rTMS relieved headaches and increased serum β endorphin levels.[56]

Noteworthy has been the observation that rTMS reverses depression associated hypo - frontalism and increases prefrontal cortex metabolism and regional blood flow.[57,58]

It has also been observed that the efficacy of rTMS for depression Is related to it's enhancement of Intrinsic functional connectivity with the subgenual cingulate.[59,60]

In summary, rTMS promotes analgesia, mood elevation, activates opioid and dopamine receptors, prefrontal cortex metabolism and regional blood flow and increases serum endorphins.

Ketamine

Ketamine an N-methyl-D-aspartate glutamate receptor antagonist and its enantiomer S- ketamine (esketamine) have been promising medications to treat treatment-resistant depression.[61-67]

Murrough et al. assessed the antidepressant effect over a 2 week period using a thrice- weekly regimen and found that response was maintained in most patients.[64] Singh et al. showed that ketamine, administered intravenously at 0.5 mg/kg of body weight either two or three times weekly, appeared comparably effective in both achieving rapid onset and maintaining antidepressant efficacy in patients with treatment-resistant depression across the 15-day period.[67]

Network dysfunction in association with altered brain levels of glutamate and gamma- aminobutyric acid have been identified in both animal and human studies of depression.[68,69,70]

Also it has been observed that an antidepressant response induced by ketamine occurs, in part, by reversing glutamatergic and gamma-aminobutyric acidergic disturbances.[67,69,70] Ketamine is an opioid agonist and its analgesic effects in rats are reversed by naltrexone, an opiate antagonist.[71] Smith et al observed that ketamine possessed agonistic, but not antagonistic, activity on opiate receptors and reported that analgesia induced by ketamine appears to be partially mediated by opiate mechanisms. Not only is its action attenuated by the narcotic antagonist naloxone, but the drug has a weak affinity for, and interacts stereoselectively at opiate receptors. It also produces a classical narcotic action on the guinea-pig ileum.[71,72,73]

Gupta et al. reported that ketamine enhances (~2- to 3-fold) the levels of opioid-induced ERK1/2 phosphorylation in recombinant as well as cells endogenously expressing μOR.

Ketamine increases the effectiveness of opiate-induced signaling by affecting multiple mechanisms (74).Of significance they suggested that because these effects were observed in heterologous cells expressing μOR ,they were independent of a non-NMDA receptor-mediated action of ketamine.[74] Also, of significance it has been demonstrated that ketamine induced respiratory depression is mediated through opioid receptors.[75]

A recent clinical study revealed a synergistic relationship between ketamine and morphine as it was observed that a small amount of ketamine enhanced morphine analgesia in postsurgical patients.[76]

Reduced GBCr (prefrontal cortex global brain connectivity with global signal) has been identified as a biomarker for depression and it has been shown that ketamine significantly increases GBCr in the PFC and reduces GBCr in the cerebellum.[77,78,79] Ketamine blocks NMDAR-dependent bursting activity to disinhibit downstream monoaminergic reward centers.[80]

Also, neuroimaging studies suggest, subanesthetic doses of Ketamine increases PFC regional cerebral blood flow, oxygen consumption, and blood volume in humans.[81]

Taken together, biochemical and neuroimaging findings suggest, ketamine has analgesic, anesthetic, antidepressant, respiratory suppressant properties. It seems that the antidepressant response of ketamine may partly be mediated through glutamate and opioid receptors and the acute effects may correspond to the prefrontal connectivity and dopamine function.

DISCUSSION

ECT, rTMS and ketamine have shown efficacy in the treatment of depression and treatment refractory depression. They also show analgesic properties independent of their antidepressant actions. This observation suggests the involvement of mu opioid receptors in ECT, TMS or ketamine induced analgesia. It seems that ECT, rTMS and ketamine elevate serum endorphin levels and TMS and ketamine independently activate prefrontal cortex metabolism and regional blood flow -in contrast to ECT which suppresses these functions.

In essence diverse and converging evidence suggests that ketamine, TMS and ECT share common biological properties to induce anesthesia, analgesia, antidepressant effect and elevation of serum endorphins. It seems that all these observations highlight the central importance of the endorphins in normal brain function, mood and pain regulation. Furthermore, it seems that the antidepressant effects of ketamine rTMS and ECT may also correspond to a triad of signature traits of anti-glutamatergic, dopaminergic and opioid agonistic influences. These Intimate associations involving glutamate opioid and dopamine pathways are worthy of emphasis especially in the context of the global connectivity and complexity of human brain function governed by the evolutionary predominant influence of prefrontal cortex.

Future studies to validate these observations and elucidate the precise mechanism of antidepressant action of various substances are warranted.

Table 1: ECT rTMS and Ketamine Effects.

	rBF* PFC	Endorphins (Serum)	Analgesia	Antidepressant	Opioid Agonism	Dopamine Agonism	NMDA-A Antagonism
ECT	-	+	+	+	+	+	+
rTMS	+	+	+	+	+	+	+
Ketamine	+	+	+	+	+	+	+

***rBF=regional blood flow**

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