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ANTIDEPRESSANT-LIKE EFFECTS OF LOW KETAMINE DOSE IS ASSOCIATED WITH INCREASED HIPPOCAMPAL AMPA/NMDA RECEPTOR DENSITY RATIO IN FEMALE WISTAR-KYOTO RATS

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Abstract

Preclinical as well as limited clinical studies indicate that ketamine, a non-competitive glutamate NMDA receptor antagonist, may exert a quick and prolonged antidepressant effect. It has been postulated that ketamine action is due to inhibition of NMDA and stimulation of AMPA receptors. Here, we sought to determine whether ketamine would exert antidepressant effects in Wistar-Kyoto (WKY) rats, a putative animal model of depression and whether this effect would be associated with changes in AMPA/NMDA receptor densities in the hippocampus. Adult female WKY rats and their control Wistar rats were subjected to acute and chronic ketamine doses and their locomotor activity (LMA) and immobility in the forced swim test (FST) were evaluated. Hippocampal AMPA and NMDA receptor densities were also measured following a chronic ketamine dose. Ketamine, both acutely (0.5–5.0 mg/kg ip) and chronically (0.5–2.5 mg/kg daily for 10 days) resulted in a dose-dependent and prolonged decrease in immobility in the FST in WKY rats only, suggesting an antidepressant-like effect in this model. Chronic treatment with an effective dose of ketamine also resulted in an increase in AMPA/NMDA receptor density ratio in the hippocampus of WKY rats. LMA was not affected by any ketamine treatment in either strain. These results indicate a rapid and lasting antidepressant-like effect of a low ketamine dose in WKY rat model of depression. Moreover, the increase in AMPA/NMDA receptor density in hippocampus could be a contributory factor to behavioral effects of ketamine. These findings suggest potential therapeutic benefit in simultaneous reduction of central NMDA and elevation of AMPA receptor function in treatment of depression.

Keywords

Depression; Ketamine; NMDA Receptor; AMPA Receptor; Hippocampus; WKY Rats

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Depression, a common, chronic and serious recurrent mental illness is estimated to affect about 17 million Americans and more than 121 million people worldwide annually. It is

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quite alarming that in the United States alone more than 30,000 of clinically depressed individuals may commit suicide in one year. Indeed, it has been estimated that the lifetime prevalence of suicide in patients suffering from affective disorders may range from 2.2 to 8.6% with the highest estimate corresponding to prior hospitalization for suicide attempts (Bostwick and Pankratz, 2000). Current medications for major mood disorders are based primarily on the biogenic amine hypothesis which posits that reduction in central levels of norepinephrine (NE), dopamine (DA) and serotonin (5HT) is responsible for the manifested symptoms. Thus drugs used for treatment of depression attempt to increase the level of these biogenic amines by various mechanisms including inhibition of the degradation or blocking the uptake of the neurotransmitters. Although these medications have had significant impact on normalizing the mood and daily functions of many individuals suffering from depression, lack of response in approximately one third of the patients, lag of onset for weeks and various side effects associated with these medications call for development of more rapid and effective pharmacotherapies (Mathew et al. 2008).

Accumulating evidence suggest that glutamatergic-based therapies might represent such an alternative (Krystal, 2008; Hashimoto, 2009; Skolnick et al. 2009). This contention is based on a number of clinical reports indicating that ketamine a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist may exert rapid and lasting antidepressant effects particularly in treatment resistant patients (Machado-Vieira et al. 2009; 2010; aan het Rot et al. 2010; Okamoto et al. 2010). Similarly, preclinical studies in various rodent models of depression indicate a quick antidepressant onset for ketamine (Maeng et al., 2008; Garcia et al. 2009; Autry et al. 2011; Li et al. 2011). Since this effect of ketamine can be blocked by an alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonist, it has been postulated that central inhibition of NMDA and stimulation of AMPA receptors may be a crucial mechanism for the antidepressant effects of ketamine (Maeng et al. 2008; Koike et al. 2011).

We have used the Wistar Kyoto (WKY) rats as a model of human depression to investigate the neurobiological substrates as well as effectiveness of novel antidepressants (Tizabi et al. 2010). WKY rats, derived from Wistar stock, show exaggerated immobility in the forced swim test (FST), reflective of their helplessness and are also prone to develop stress-induced anxiety-like characteristics (Soderpalm, 1989; Paré and Redei, 1993; Pini et al. 1997). Similar to what is seen in human population, these rats also show pattern of sleep disruption including an increase in total REM sleep and increased sleep fragmentation (Dugovic et al. 2000). Interestingly, treatment of WKY rats with tricyclic antidepressants (e.g. desipramine), but not selective serotonin reuptake inhibitors (e.g. fluoxetine or paroxetine) result in a reduction of their immobility in the FST. This has led to the suggesting that WKY rats may be a suitable model for at least a subset of treatment resistant depression (Griebel et al. 1994; Lahmame et al. 1997; Lopez-Rubalcava and Lucki, 2000; Tejani-Butt et al. 2003; Tizabi et al. 2010).

In this study we sought to determine whether WKY rats would respond to ketamine and whether hippocampal AMPA/NMDA receptor densities would be affected by ketamine treatment. We selected hippocampus because of its critical role in mood regulation and postulated role of this area in effectiveness of many antidepressants (Fournier and Duman, 2011; Kohli et al. 2011; MacQueen and Frodl, 2011). Our major hypothesis was that ketamine would impart a dose-dependent and long lasting antidepressant effect in WKY rats. Moreover we postulated that antidepressant-like effects of chronic ketamine would be associated with an increase in the ratio of AMPA/NMDA receptor densities in the hippocampus.

2. EXPERIMENTAL PROCEDURES

2.1 Animals

Age matched adult female WKY and Wistar rats (Harlan Laboratories, Indianapolis, IN) were used throughout the study. We selected female rats because despite higher prevalence of depression in women few studies are conducted in this gender (Herzog et al. 2009). Moreover, parallel to what is seen in human population (Kessler et al. 1993; Meagher and Murray, 1997) the female WKY rats show a higher incidence of depressive-like behavior compared to the male rats of the same strain (Paré and Redei, 1993). Animals were housed in groups of four in standard polypropylene shoebox cages ($42 \times 20.5 \times 20$ cm) on hardwood chip bedding (alpha-dry) in a room designated for female rats. Animals had access to food (Harlan Tek Lab) and water ad libitum. The room was maintained at $24\text{--}26^\circ\text{C}$ at $51\text{--}66\%$ relative humidity, on a 12-h reversed light/dark cycle (lights on at 19.00 hr). The reversal of time cycle was to allow convenient measurement of the behavior in active (dark) phase of the light cycle. All experiments were carried out in accordance with NIH guidelines as approved by the Institutional Animal Care and Use Committee.

To acclimate the subjects to housing conditions, animals arrived at least one week prior to testing. During this period, they were gentled once daily in order to minimize any stress that might result from routine handling. Behaviors were evaluated in the early part of the dark phase between 09:00 A.M. and 12:00 P.M using a red light as source of illumination. Different groups of rats were used for different dose treatments. Similarly, a separate group of animals was used for receptor binding measurements.

2.2 Drug Treatment and Behavioral Testing

For acute studies, groups of rats were injected intraperitoneally (ip) with saline (control) or a dose of ketamine (0.5, 2.5 and 5.0 mg/kg) and were tested 20 min later for open field locomotor activity (LMA) followed by the forced swim test (FST). Ketamine HCl was purchased from Henry Schein (Melville, NY). The locomotor activity test was conducted for 10 min and immediately after that the FST was conducted for 5 min. For chronic studies, the animals were injected with saline or a dose of ketamine (0.5 or 2.5 mg/kg ip) daily (around noon) for 10 days and the behavioral tests for LMA and FST were conducted 20–22 hr after the last injection. The same animals were tested a week or two later to determine the lasting effects of treatments.

2.3 Locomotor Activity (LMA) Monitoring

Locomotor activity was measured first for each animal during a 10 minute period. An open-field activity monitoring cage ($27 \times 27 \times 20.3$ cm, Med Associates, Inc., St. Albans, VT) was used to assess activity. Ambulatory counts representing the number of infrared beam interruptions were recorded.

2.4 Forced Swim Test (FST)

The method of Porsolt et al. (1977) with modification by Detke et al. (1995) was used to assess the immobility of the rats as a measure of their helplessness or depressive-like behavior. It should be noted that WKY rats exhibit spontaneous immobility in the forced swim test; hence, there is no need to have a pretest exposure to forced swimming the day before as is customary in inducing helplessness in other strains (Tejani-Butt et al. 2003; Getachew et al. 2008; Tizabi et al. 2010; Hauser et al. 2011). Immediately after the LMA test, the rat was placed in a round Pyrex cylinder pool measuring 17 cm in diameter and 60 cm in height for 5 min. The cylinder was filled with 30 cm water ($25 \pm 1^\circ\text{C}$) to ensure that the animal could not touch the bottom of the container with its hind paws or its tails (Lucki, 1997). The animal's FST activity was video recorded for subsequent analysis (Tizabi et al.

2010; Hauser et al. 2011). The rat was removed after 5 min, dried, and placed in its home cage.

A time sampling scoring technique was used whereby the predominant behavior in each 5-s period of the 300-s test was recorded. Inactivity (immobility) and swimming were distinguished as mutually exclusive behavioral states. Swimming behavior was defined as movement (usually horizontal) throughout the cylinder. Immobility was defined when no additional activity was observed other than that required to keep the rat's head above the water.

2.5 Tissue Preparation

For neurochemical evaluations, animals were treated chronically with 0.5 mg/kg ketamine daily for ten days and were sacrificed by decapitation 20 hr after the last injection. This dose and duration was chosen to coincide with the lowest effective chronic dose of ketamine as an antidepressant. The brains were rapidly removed, frozen on dry ice and stored at -80°C . Each frozen brain was later thawed on ice and hippocampus (bilateral) was dissected alternating between treatment groups as described previously (Tizabi et al. 1999, 2001). For receptor binding, tissue was homogenized in 10 volumes of ice-cold buffer (50 mM Tris-HCl, 3 mM MgCl_2 , and 1 mM EGTA, pH 7.4) and centrifuged at $48,000\times g$ at 4°C for 30 min. The pellet was washed twice by suspension in the same buffer followed by centrifugation. The final pellet was re-suspended in (50 mM Tris-HCl, 3 mM MgCl_2 , and 1 mM EGTA, and 100 mM NaCl, pH 7.4). Aliquots of re-suspended membranes were used for measurement of total protein and receptor binding densities.

2.6 NMDA Binding Assay

NMDA (N-methyl-D-aspartate) receptor density was measured in membrane preparations using [^3H]MK801 as a ligand as described by Berger (2000). [^3H]MK801 (specific activity 27.5 Ci/mmol) was purchased from Perkin-Elmer, Boston, MA. Briefly, membrane preparations containing 15–20 μg of protein was incubated in a reaction volume (250 μl) containing 5 nM [^3H]MK801 in 50 mM Tris-acetate buffer pH 7.0 in presence of 10 μM glutamate and 10 μM glycine for 2 hrs at room temperature. Binding reactions were started by the addition of tissue and terminated by vacuum filtration through Whatman GF/C filters, which were mounted on a Brandel cell harvester and pre wetted with 0.5% polyethylenimine to reduce binding to the filter. The filters were washed three times with 4 mL aliquots of buffer and then counted in a Micro β scintillation counter. Non-specific binding in all assays was determined in presence of 10 mM glutamate. Specific binding was defined as the difference between total binding and non-specific binding. Protein analysis was performed by Pierce protein assay using BCA reagent. Final receptor density was expressed as femto mole labeled MK-801/mg protein (fmole/mg Pr).

2.7 AMPA Binding Assay

AMPA receptor density was measured in membrane preparations using [^3H] AMPA as a ligand as described by Wenk and Barnes (2000) with minor modifications. [^3H]AMPA (specific activity~ 40 Ci/mmol) was purchased from Perkin-Elmer, Boston, MA. Briefly, membrane preparations containing 15–20 μg of protein was incubated in a reaction volume (250 μl) containing 15 nM [^3H]AMPA in 50 mM Tris-acetate buffer pH 7.2 containing 2.5 mM CaCl_2 , 0.05 mM EGTA and 50 mM KSCN for 2 hrs at room temperature. Binding reaction was started by the addition of tissue and terminated by vacuum filtration through Whatman GF/C filters similar to the procedure for NMDA binding assay described above. Here also the final result was expressed as femto mole labeled AMPA/mg protein (fmole/mg Pr).

2.8 Statistical Analysis

Statistical differences between treatment groups were determined by two-way ANOVA followed by post-hoc Newman-Keuls Multiple comparison test to determine which groups differed. Significant difference was considered a priori at $p < 0.05$. Data were analyzed using Graphpad Prism 3 (Graphpad Software, Inc, San Diego, CA, USA).

3. RESULTS

3.1 Behavioral Results

Figure 1A depicts the acute effects of various doses of ketamine on immobility in the FST in female WKY and Wistar rats. Ketamine treatment resulted in a dose-dependent reduction in immobility in WKY rats without affecting the FST immobility in Wistar rats. FST immobility in WKY rats was not significantly affected by 0.5 mg/kg ketamine dose, but was reduced by approximately 38% ($p < 0.05$) with 2.5 mg/kg and by approximately 62% ($p < 0.01$) with 5.0 mg/kg dose, which was similar to basal immobility in the Wistar rats. Open field locomotor activity was not affected by ketamine treatment in either strain (Fig 1B), suggesting that the effects in the FST were independent of general locomotor activity. The animals that were affected by ketamine doses were tested a week later to determine whether the effects on immobility in the FST persisted. Ketamine's effect at the lower dose of 2.5 mg/kg was absent after one week of rest, but the effect of 5 mg/kg was still evident ($p < 0.05$) at this time point (Fig 1C). At two weeks post treatment the effect of 5 mg/kg ketamine had also dissipated (data not shown). Locomotor activity remained unaffected (data not shown).

Figure 2A depicts the effects of two chronic doses of ketamine (daily injection for 10 days) on immobility in the FST in female WKY and Wistar rats. Ketamine at both doses of 0.5 mg/kg and 2.5 mg/kg caused significant reduction ($p < 0.01$) in immobility in WKY rats without affecting the Wistar rats. Open field locomotor activity was not affected by ketamine treatment in either strain (Fig 2B). Ketamine's effect at the lower dose of 0.5 mg/kg was absent after one week of rest, but the effect of 2.5 mg/kg was still evident ($p < 0.05$) at this time point (Fig 2C). At two weeks post treatment the effect of 2.5 mg/kg ketamine had also dissipated (Fig 2C). Locomotor activity remained unaffected (data not shown).

3.2 Receptor Binding Results

Figure 3A depicts the effects of chronic ketamine (0.5 mg/kg daily for 10 days) on hippocampal NMDA (Fig 3A) and AMPA (Fig 3B) receptor densities in WKY and Wistar rats. There were no significant differences in basal densities of either receptor between WKY and Wistar rats. Ketamine treatment resulted in approximately 17% decrease in NMDA receptor density in WKY rats and approximately 14% decrease in Wistar rats, neither one of which was statistically significant. However, ketamine treatment resulted in approximately 26% increase in AMPA receptor density ($p < 0.05$) in WKY rats only. AMPA receptor densities in Wistar rats were not affected by ketamine treatment. Thus, chronic ketamine caused an increase in the hippocampal AMPA/NMDA receptor density ratio in WKY rats only (Fig 3C).

4. DISCUSSION

The results of this study confirm a rapid and lasting antidepressant-like effect of a relatively low ketamine dose in WKY rat model of depression. Moreover, the antidepressant effect of a chronic low regimen of ketamine was associated with an increase in the AMPA/NMDA receptor density ratio in the hippocampus. Previous reports indicate that the antidepressant effects of ketamine can be blocked by AMPA antagonists (Maeng et al., 2008; Koike et al.

2011) suggesting that the effects of ketamine may be mediated by increases in AMPA-to-NMDA glutamate receptor throughput in critical neuronal circuits (Maeng et al. 2008; Machado-Vieira et al. 2009a,b). Thus, chronic ketamine appears to exert its effects by shifting the receptor density composition such that an increase in AMPA function may accompany simultaneous inhibition of NMDA receptors.

The acute effect of ketamine is most likely due to potent inhibition of NMDA receptor function and is unlikely to result in increase in AMPA receptor density as such adaptive mechanism and formation of new protein would require several days, although this assertion needs to be verified in future studies. Curiously, a previous study evaluating the basal NMDA receptor density in male WKY and Wistar rats found a significant decrease in hippocampal CA1 region of WKY rats without any notable effects in CA2, CA3 or dentate gyrus (Lei et al. 2009). It is likely that our lack of finding of any significant difference in NMDA receptor density between WKY and Wistar rats was due to inclusion of the entire hippocampus which could mask detection of significant differences in a specific sub-region. Moreover, the effects of gender difference cannot be ruled out (Holtman et al. 2003) as our study was carried out in female rats whereas the study by Lei et al. (2003) was carried out in male rats.

Previous studies using subanesthetic doses of ketamine had reported an antidepressant effect of ketamine in mice using the learned helplessness, forced swim, and passive avoidance tests (Maeng et al. 2008). Similarly, ketamine at relatively high dose of 10–15 mg/kg reversed the anhedonia-like behavior induced by chronic mild or unpredictable stress in rats (Garcia et al. 2009; Li et al. 2011). The dose and treatment regimen with ketamine is a crucial consideration as high doses of ketamine (50–160 mg/kg) might not only be associated with severe side effects, but may also not result in significant or lasting antidepressant-like effects (Popik et al. 2009). It is important to note that in our study ketamine did not exert any behavioral changes in the control group, the Wistar rat. This observation is in line with previous reports indicating that ketamine was without effect in naïve mice (Popik et al. 2009). The lack of ketamine effect in Wistar rats in our study could also be attributed to the flooring effect in immobility scores in these rats. WKY rats, on the other hand, may be considered an animal model of treatment resistant, in at least a subpopulation of depressed patients, as these rats do not respond to selective serotonin reuptake inhibitors (Griebel et al. 1994; Lahmame et al. 1997; Lopez-Rubalcava and Lucki, 2000; Tejani-Butt et al. 2003). Thus, it is of significant importance that ketamine has been shown to be effective in some treatment-resistant patients (Liebrenz et al. 2009; Mathew et al. 2009; Price et al. 2009; aan het Rot et al. 2010; Okamoto et al. 2010).

The adverse effects of ketamine at anesthetic or even subanesthetic doses are well documented. In fact, ketamine and other NMDA antagonists have been used extensively in animals to model symptoms of psychosis in humans (reviewed in Tizabi, 2007). The dose used in our study is low enough not to be associated with such adverse reactions. Moreover, it has been reported that intravenous administration of ketamine at (0.5 mg/kg) in humans has the rapid desirable antidepressant effect without notable adverse reactions (Zarate et al. 2006; Machado-Vieira et al. 2009a,b; aan het Rot et al. 2010). Indeed, it has been proposed that ketamine may be a useful drug in reducing suicidal ideation in severely depressed patients resistant to other antidepressants (Liebrenz et al. 2009; Mathew et al. 2009; Price et al. 2009; aan het Rot et al. 2010; Okamoto et al. 2010). It should be noted that ketamine or similar drugs may also be useful as an adjunct therapy with other antidepressants (Ghasemi et al. 2009). Although it is well recognized that ketamine's major mechanism of action involves NMDA receptor inhibition, ketamine might also interact with other receptors or neuromodulators including dopamine D2, muscarinic cholinergic receptors, μ opioids receptors and GABA (A) receptors (Hirota et al. 2004; Hevers et al. 2008; Tan et al. 2011).

and calcium influx (Sikand et al. 1995). It remains to be determined to what extent such non-glutamatergic interactions may be contributing to the therapeutic or adverse effects of ketamine. Furthermore, in addition to the glutamatergic ionotropic receptors, metabotropic glutamate receptors may also play a role in mood disorders (Witkin et al. 2007). Interestingly, the antidepressant effects of various metabotropic receptor agonists could also be blocked by AMPA antagonist, suggesting that their action may be similar to ketamine. Thus, glutamatergic neurotransmission in general and AMPA-NMDA receptors in particular may be suitable targets for development of novel antidepressants. In this regard it is of interest to note that compounds that enhance neuronal function via AMPA receptor stimulation (ampakines) may also exert antidepressant effects in animal models of depression (Machado-Vieira et al. 2006, see also review by Bleakman et al. 2007).

Although the exact mechanism leading to the increase in hippocampal AMPA/NMDA receptor density following chronic ketamine treatment in our paradigm is not at hand, it has been postulated that ketamine may enhance AMPA receptor trafficking into post-synaptic membrane (Machado-Vieira et al. 2006). It would be of significant interest to elucidate whether such interaction of NMDA and AMPA constitutes a compensatory mechanism or whether combination of an NMDA antagonist with an AMPA agonist may offer a more effective intervention in treatment-resistant depression.

5. CONCLUSIONS

In summary, our results suggest a quick and long lasting antidepressant effect of relatively low doses of ketamine in WKY rat model of depression. Moreover, the observed increase in hippocampal AMPA/NMDA receptor density could be a contributory factor to the observed behavioral effects of ketamine.

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HIGHLIGHTS

- Low dose ketamine elicits a rapid and lasting antidepressant-like effect in WKY rats
- Low dose ketamine enhances hippocampal AMPA receptor density in WKY rats
- Low dose ketamine has no effect on AMPA receptor density in Wistar rats
- Low dose ketamine increases hippocampal AMPA/NMDA receptor density in WKY rats

Figure 1A

Figure 1B

Figure 1C

Fig 1.

Fig 1A: Effect of acute treatment of ketamine on FST immobility in WKY and Wistar rats. Values are mean $\pm$ SEM, * p <0.05, ** p <0.01 compared to SAL. n =7–8/group.

Fig 1B: Effect of acute ketamine treatment on open field locomotor activity in WKY and Wistar rats. Values are mean $\pm$ SEM, n =7–8.

Fig 1C: Effect of acute ketamine on FST immobility in WKY rats after one week of rest. Values are mean $\pm$ SEM, * p <0.05 compared to Sal. n =7–8

Figure 2A

Figure 2B

Figure 2C

Fig 2.

Fig 2A: Effect of chronic ketamine treatment on FST immobility in WKY and Wistar rats. Values are mean $\pm$ SEM, * p <0.05, ** p <0.01 compared to Sal. n =7–8

Fig 2B: Effect of chronic ketamine treatment on open field locomotor activity in WKY and Wistar rats. Values are mean $\pm$ SEM, n =7–8

Fig 2C: Effect of chronic ketamine on FST in WKY rats after one and two weeks of rest. Values are mean $\pm$ SEM, * p <0.05 compared to Sal. n =7–8

Figure 3A

Figure 3B

Figure 3C

Fig 3.

Fig 3A: Effect of chronic ketamine treatment (0.5 mg/kg for 10 days) on hippocampal NMDA receptor densities in WKY and Wistar rats. Values are mean $\pm$ SEM, n=7–8

Fig 3B: Effect of chronic ketamine treatment (0.5 mg/kg for 10 days) on hippocampal AMPA receptor densities in WKY and Wistar rats. Values are mean $\pm$ SEM, *p<0.05 compared to Sal. n=7–8

Fig 3C: Effect of chronic ketamine treatment (0.5 mg/kg for 10 days) on hippocampal AMPA/NMDA ratio in WKY and Wistar rats. Values are mean $\pm$ SEM, *p<0.05 compared to Sal. n=7–8