**Supplementary Table S1**. Behavioural Effects of Ketamine in Preclinical Models

| Citation | Animal | Strain | M/F | Dose in mg/kg *Enantiomer* | Stress Model | Time of Testing (after last injection) | Tests | Behavioural Responses, time (dose) | Injection Method | Special Notes/Considerations |
|---|---|---|---|---|---|---|---|---|---|---|
| (Autry et al., 2011) | Mouse | C57BL/6 | M | 3 *(R,S)-ketamine* | Naïve | 30min, 24h (FST) | FST | • FST: ↓ Immobility, 30min-24h | IP | |
| (Carrier and Kabbaj, 2013) | Rat | Sprague Dawley | M | 2.5, 5, 10 *(R,S)-ketamine* | Naïve | 30min (FST)<br>30min (NSF)<br>30min (LDB)<br>24h (EPM)<br>48h (SPT) | FST<br>NSF<br>LDB<br>EPM<br>SPT | • FST: ↓ Immobility (5, 10)<br>• NSF: ↓ Latency (5, 10)<br>• LDB: = Time spent and number of entries into light box<br>• EPM: = Time spent and number of entries into open arms<br>• SPT: ↑ Sucrose preference (5, 10) | IP | |
| (Carrier and Kabbaj, 2013) | Rat | Sprague Dawley | F | 2.5, 5, 10 *(R,S)-ketamine* | Naïve | 30min (FST)<br>30min (NSF)<br>30min (LDB)<br>24h (EPM)<br>48h (SPT) | FST<br>NSF<br>LDB<br>EPM<br>SPT | • FST: ↓ Immobility (2.5, 5, 10)<br>• NSF: ↓ Latency (2.5, 5, 10)<br>• LDB: = Time spent and number of entries into light box<br>• EPM: = Time spent and number of entries into open arms<br>• SPT: = Sucrose preference | IP | Estrus cycle not taken into account. |
| (Chang et al., 2018) | Mouse | C57BL/6J | M/F | 3, 10 *(R)-ketamine* | LPS | 1h (LMT)<br>3h (FST) | LMT<br>FST | • LMT: = Locomotion<br>• FST: ↓ Immobility (10)<br>No differences between M/F in terms of acute antidepressant response. | IP | Estrus cycle not taken into account. |
| (Dossat et al., 2018) | Mouse | C57BL/6J | M | 1.5, 3 *(R,S)-ketamine* | Naïve | 30min (FST) | FST | • FST: ↓ Immobility (3) | IP | |
| (Dossat et al., 2018) | Mouse | C57BL/6J | F | 1.5, 3 *(R,S)-ketamine* | Naïve | 30min (FST) | FST | • FST: ↓ Immobility (D1: 3; PE: 1.5, 3) | IP | Giving an ERα/β agonist was sufficient to increase behavioural sensitivity in D1 females.<br>Increased sensitivity in PE is mirrored by activation of Akt in the PFC and Akt/CaMKIIα in the HC. |
| (Franceschelli et al., 2015) | Mouse | C57BL/6J | M | 3, 5, 10 *(R,S)-ketamine* | Naïve | 30min, 24h (FST) | FST | • FST: ↓ Immobility, 30min (5, 10)<br>• FST: ↓ Immobility, 24h (10) | IP | |
| (Franceschelli et al., 2015) | Mouse | C57BL/6J | F | 3, 5, 10 *(R,S)-ketamine* | Naïve | 30min, 24h (FST) | FST | • FST: ↓ Immobility, 30min (3, 5, 10)<br>• FST: ↓ Immobility, 24h (5, 10) | IP | Estrus cycle not taken into account. |
| (Franceschelli et al., 2015) | Mouse | C57BL/6J | M | 10 *(R,S)-ketamine* | CMS | 30min (OFT)<br>1d, 7d (FST)<br>4d (MBT)<br>5d (SplT)<br>6d (SPT) | OFT<br>FST<br>MBT<br>SplT<br>SPT | OFT: = Locomotor activity and center arena exploration<br>FST: ↓ Immobility, 1d-7d<br>MBT: = Number of marbles buried<br>SplT: ↑ Grooming duration<br>SPT: = Sucrose preference | IP | |

| **Citation** | **Animal** | **Strain** | **M/F** | **Dose in mg/kg** ***Enantiomer*** | **Stress Model** | **Time of Testing (after last injection)** | **Tests** | **Behavioural Responses, time (dose)** | **Injection Method** | **Special Notes/Considerations** |
|---|---|---|---|---|---|---|---|---|---|---|
| (Franceschelli et al., 2015) | Mouse | C57BL/6J | F | 10<br>*(R,S)-ketamine* | CMS | 30min (OFT)<br>1d, 7d (FST)<br>4d (MBT)<br>5d (SplT)<br>6d (SPT) | OFT<br>FST<br>MBT<br>SplT<br>SPT | OFT: ↓ Locomotor activity and center arena exploration<br>FST: ↓ Immobility, 1d<br>MBT: = Number of marbles buried<br>SplT: = Grooming duration<br>SPT: = Sucrose preference | IP | Estrus cycle not taken into account. |
| (Garcia et al., 2008a) | Rat | Wistar | M | 5, 10, 15; 14d<br>Once Daily<br>*(R,S)-ketamine* | Naïve | Day 12 (OFT)<br>Day 13, 14 (FST)<br>All tests 60min after drug administration | FST<br>OFT | • FST: ↓ Immobility, ↑ Climbing, ↑ Swimming (5, 10, 15)<br>• OFT: = Number of rearings, = Number of crossings | IP | Acute administration of 5mg/kg in rats is insufficient for a behavioural response, but it is sufficient in a chronic regimen. |
| (Garcia et al., 2008b) | Rat | Wistar | M | 5, 10, 15<br>*(R,S)-ketamine* | Naïve | 60min (FST)<br>60min (OFT) | FST<br>OFT | • FST: ↓ Immobility (10, 15)<br>• OFT: = Number of rearings, = Number of crossings | IP | |
| (Garcia et al., 2009) | Rat | Wistar | M | 15; acute<br>*(R,S)-ketamine* | Naïve | 60min (SPT) | SPT | • SPT: = Sucrose preference | IP | |
| (Garcia et al., 2009) | Rat | Wistar | M | 15; 7d<br>Once Daily<br>*(R,S)-ketamine* | Naïve | 60min (SPT) | SPT | • SPT: ↑ Sucrose preference | IP | Larger differences in chronic than acute ketamine administration. |
| (Garcia et al., 2009) | Rat | Wistar | M | 15; acute<br>*(R,S)-ketamine* | CMS | 60min (SPT) | SPT | • SPT: = Sucrose preference | IP | |
| (Garcia et al., 2009) | Rat | Wistar | M | 15; 7d<br>Once Daily<br>*(R,S)-ketamine* | CMS | 60min (SPT) | SPT | • SPT: ↑ Sucrose preference | IP | |
| (Guo et al., 2016) | Rat | Sprague Dawley | M/F | 6-14; 9d<br>(Once daily)<br>*(R,S)-ketamine* | Naïve | Day 9 (CPP) | CPP | • CPP: ↑ Preference (NS)<br>Females more sensitive to the ketamine-induced CPP than males. Positive reinforcement agent in both sexes, but preference scores were much higher in females. | NS | Estrus cycle not taken into account. |
| (Iñiguez et al., 2018) | Mouse | C57BL/6J | F | 20<br>3 injections<br>*(R,S)-ketamine* | ES | 30min (SIT) | SIT | • SIT: ↑ Social interaction<br>• ES induced avoidance behaviour, which was rescued with ketamine | IP | Estrus cycle not taken into account. |
| (Li et al., 2010) | Rat | Sprague Dawley | M | 10<br>*(R,S)-ketamine* | IES | 24h (FST)<br>24h (NSF)<br>24h (LH)<br>30min, 1h, 2h, 6h, | FST<br>NSF<br>LH | • FST: ↓ Immobility<br>• NSF: ↓ Latency to eat<br>• LH: ↓ Number of escape failures | IP | |
| (Li et al., 2011) | Rat | Sprague Dawley | M | 10<br>*(R,S)-ketamine* | CUS | 1d, 3d, 5d, 7d (SPT)<br>2d (NSF) | SPT<br>NSF | • SPT: ↑ Sucrose preference, 3d-7d<br>• NSF: ↓ Latency | IP | |

| Citation | Animal | Strain | M/F | Dose in mg/kg *Enantiomer* | Stress Model | Time of Testing (after last injection) | Tests | Behavioural Responses, time (dose) | Injection Method | Special Notes/Considerations |
|---|---|---|---|---|---|---|---|---|---|---|
| (McDougall et al., 2017) | Rat | Sprague Dawley | M/F | 5, 10, 20, 40 *(R,S)-ketamine* | Naïve | Immediate (LMT) | LMT | • LMT: ↑ Locomotion<br>• Significantly more locomotor activity and motor disrupting effects in female adolescent rats than male adolescent rats injected with (20, 40). | IP | |
| (Saland et al., 2016) | Rat | Sprague Dawley | M | 2.5; on days 4 and 6 (of 6) *(R,S)-ketamine* | Naïve | 24h-7d (SPT)<br>Tested once daily | SPT | • SPT: = Sucrose preference | IP | Increase in sucrose preference (lasting 6 days) if given cyclic P4. |
| (Saland et al., 2016) | Rat | Sprague Dawley | F | 2.5; on days 4 and 6 (of 6) *(R,S)-ketamine* | Naïve | 24h-7d (SPT)<br>Tested once daily | SPT | • SPT: ↑ Sucrose preference, 24h-7d | IP | OVX animals with E2/P4 hormone replacement to physiological levels. |
| (Sarkar and Kabbaj, 2016) | Rat | Sprague Dawley | M | 2.5, 5 *(R,S)-ketamine* | CSIS | 3h, 24h (SPT)<br>3d (FST) | SPT<br>FST | • SPT: ↑ Sucrose preference, 3h (5)<br>• FST: ↓ Immobility (5) | NS | |
| (Sarkar and Kabbaj, 2016) | Rat | Sprague Dawley | F | 2.5, 5 *(R,S)-ketamine* | CSIS | 3h, 24h (SPT)<br>3d (FST) | SPT<br>FST | • SPT: = Sucrose preference<br>• FST: ↓ Immobility (2.5, 5) | NS | Females injected with ketamine during D1. No reduction in SPT after stress, but also no increase after ketamine. |
| (Schoepfer et al., 2019) | Rat | Sprague Dawley | M | 2.5, 5, 10; 10d Every other day *(R,S)-ketamine* | Naïve | Day 11 (CPP)<br>Day 2, 12 (LMT) | LMT<br>CPP | • LMT: ↑ Locomotion, day 12 (5, 10)<br>• Locomotor response to 5mg/kg significantly smaller in males than females on day 12<br>• CPP: ↑ Preference (10) | IP | |
| (Schoepfer et al., 2019) | Rat | Sprague Dawley | F | 2.5, 5, 10; 10d Every other day *(R,S)-ketamine* | Naïve | Day 11 (CPP)<br>Day 2, 12 (LMT) | LMT<br>CPP | • LMT: ↑ Locomotion, day 2 and 12 (5, 10)<br>• Locomotor response to 5mg/kg significantly larger in females than males on day 12<br>• CPP: = Preference | IP | Females have more psychostimulant effects at an equivalent dose as males, but they have a lower threshold for antidepressant effects and therefore may be more tolerant to effects at lower doses.<br>Estrus cycle not taken into account. |
| (Silvestre et al., 1997) | Rat | Wistar | M | 7 *(R,S)-ketamine* | Naïve | 30min (EPM)<br>30min (SIT)<br>30min (HBT) | EPM<br>SIT<br>HBT | • EPM: ↓ Time spent and number of entries into open arms<br>• SIT: ↓ Interaction, ↓ Rearings, ↓ Activity in medial areas, ↓ Total central activity<br>• HBT: ↑ Crossings, ↓ Rearings | IP | Anxiogenic-like effects. |

| Citation | Animal | Strain | M/F | Dose in mg/kg *Enantiomer* | Stress Model | Time of Testing (after last injection) | Tests | Behavioural Responses, time (dose) | Injection Method | Special Notes/Considerations |
|---|---|---|---|---|---|---|---|---|---|---|
| (Strong et al., 2017) | Rat | Sprague Dawley | M | 2.5, 5; 1/wk for 7 wk<br>*(R,S)-ketamine* | Naïve | Immediate (LMT)<br>3-4d (CPP)<br>2wk (Ketamine challenge using escalating doses of 0, 2.5, and 5mg/kg every 30 mins) | LMT<br>CPP<br>KC | • LMT: ↑ Locomotion, 10min (2.5, 5)<br>• KC: Locomotor sensitization when treated with (5) and challenged with (5)<br>• CPP: = Preference | IP | |
| (Strong et al., 2017) | Rat | Sprague Dawley | F | 2.5, 5; 1/wk for 7 wk<br>*(R,S)-ketamine* | Naïve | Immediate (LMT)<br>3-4d (CPP)<br>2wk (Ketamine challenge using escalating doses of 0, 2.5, and 5mg/kg every 30 mins) | LMT<br>CPP<br>KC | • LMT: ↑ Locomotion, 10min-20min (2.5)<br>• KC: Locomotor sensitization when treated with (2.5, 5) and challenged with (5)<br>• CPP: ↓ Preference (5) (CPA) | IP | All females were tested in D1. |
| (Thelen et al., 2016) | Mouse | C57BL/6J | M | 3, 5, 10; 21 d<br>Once daily<br>*(R,S)-ketamine* | Naïve | Day 15 (OFT)<br>Day 22 (FST) | OFT<br>FST | • OFT: = Center arena exploration<br>• FST: ↓ Immobility (10) | IP | |
| (Thelen et al., 2016) | Mouse | C57BL/6J | F | 3, 5, 10; 21 d<br>Once daily<br>*(R,S)-ketamine* | Naïve | Day 15 (OFT)<br>Day 22 (FST) | OFT<br>FST | • OFT: ↓ Center arena exploration (5, 10)<br>• FST: ↑ Immobility (10) | IP | Repeated ketamine induced anxiety-like and depressive-like effects in females, but not males.<br>Estrus cycle not taken into account. |
| (Tizabi et al., 2012) | Rat | Wistar-Kyoto (WKY) | F | 2.5, 5.0<br>*(R,S)-ketamine* | Naïve | 20min, 1wk (FST)<br>20min, 1wk (OFLA) | FST<br>OFLA | • FST: ↓ Immobility, 20min (2.5, 5)<br>• FST: ↓ Immobility, 20min-1wk (5)<br>• OFLA: = Locomotor activity | IP | |
| (Tizabi et al., 2012) | Rat | Wistar | F | 2.5, 5.0<br>*(R,S)-ketamine* | Naïve | 20min, 1wk (FST)<br>20min, 1wk (OFLA) | FST<br>OFLA | • FST: = Immobility<br>• OFT: = Locomotor activity | IP | |
| (Tizabi et al., 2012) | Rat | Wistar-Kyoto (WKY) | F | 0.5, 2.5; 10d<br>Once daily<br>*(R,S)-ketamine* | Naïve | 20-22h, 1wk (FST)<br>20-22h, 1wk (OFLA) | FST<br>OFLA | • FST: ↓ Immobility 20-22h (0.5, 2.5)<br>• FST↓ Immobility, 20-22h-1wk (2.5)<br>• OFLA: = Locomotor activity | IP | |
| (Tizabi et al., 2012) | Rat | Wistar | F | 0.5, 2.5; 10d<br>Once daily<br>*(R,S)-ketamine* | Naïve | 20-22h, 1wk (FST)<br>20-22h, 1wk (OFLA) | FST<br>OFLA | • FST: = Immobility<br>• OFLA: = Locomotor activity | IP | |
| (Wright et al., 2017) | Rat | Sprague Dawley | M | <u>Self-administration:</u><br>0.1/infusion (every 4 days; 10 sessions)<br><u>Reinstatement:</u><br>2.5<br>*(R,S)-ketamine* | Naïve | Daily extinction training. Once established, reinstatement dose administered immediately before session. | | Reinstated ketamine-seeking behaviours after extinction when exposed to drug-paired cues alone or ketamine+cues. | IV<br>IP | Self-administration. The cues alone were enough to reinstate deug seeking behaviours in males. |

| Citation | Animal | Strain | M/F | Dose in mg/kg<br>*Enantiomer* | Stress Model | Time of Testing (after last injection) | Tests | Behavioural Responses, time (dose) | Injection Method | Special Notes/Considerations |
|---|---|---|---|---|---|---|---|---|---|---|
| (Wright et al., 2017) | Rat | Sprague Dawley | F | Self-administration:<br>0.1/infusion<br>(every 4 days; 10 sessions)<br>Reinstatement:<br>2.5<br>*(R,S)-ketamine* | Naïve | Daily extinction training. Once established, reinstatement dose administered immediately before session. | | Diestrus trained: failed to acquire ketamine self-administration after ketamine/drug-paired cue exposure and rapidly decrease intake.<br>Proestrus trained: Reinstated ketamine-seeking behaviours after extinction when exposed to drug-paired cues alone or ketamine+cues. | IV<br>IP | Self-administration.<br>Females lavaged for estrus staging.<br>The cues alone were enough to reinstate drug seeking behaviours in PE-trained, but not D1-trained, animals |
| (Yang et al., 2015) | Mouse | C57BL/6 | M | 10<br>*(R)-ketamine*<br>*(S)-ketamine* | SDS | 1d, 6d (SPT)<br>2d, 7d (TST)<br>2d, 7d (FST) | SPT<br>TST<br>FST | • SPT: ↑ Sucrose preference, 1d-6d<br>• TST: ↓ Immobility, 2d-7d<br>• FST: ↓ Immobility, 2d-7d<br>(R)- and (S)-ketamine both work, but (R)-ketamine has a greater effect in all tests. | IP | R-ketamine more potent than S-ketamine.<br>(S)-ketamine increases locomotion, has psychomimetic effects, and induces CPP, where (R)-ketamine doesn't seem to do any of those things in mice.<br>(R)-ketamine may be free of psychomimetic side effects and abuse liability in humans. |
| (Yang et al., 2015) | Mouse | C57BL/6 | M | 5, 10, 20, 7d (CPP)<br>On days 1, 3, 5<br>(R)-ketamine (5, 10, 20)<br>(S)-ketamine (5, 10, 20)<br>(R,S)-ketamine (10)<br><br>5, 10, 20 (LMT, PPI)<br>(R)-ketamine<br>(S)-ketamine | SDS | 7d | LMT<br>PPI<br>CPP | *(S)-ketamine*<br>• LMT: ↑ Locomotion (5, 10, 20)<br>• PPI: Deficits at 77db and 71db (10, 20)<br>• CPP: ↑ Preference (5, 10, 20)<br><br>*(R)-ketamine*<br>• LMT: = Locomotion<br>• PPI: Normal<br>• CPP: = Preference<br><br>*(R,S)-ketamine*<br>• CPP: ↑ Preference | IP | R-ketamine more potent than S-ketamine.<br>(S)-ketamine increases locomotion, has psychomimetic effects, and induces CPP, where (R)-ketamine doesn't seem to do any of those things in mice.<br>(R)-ketamine may be free of psychomimetic side effects and abuse liability in humans. |
| (Yang et al., 2015) | Rat | Sprague Dawley | M | 20<br>*(R)-ketamine*<br>*(S)-ketamine* | US | 5d (LH) | LH | LH: ↓ Escape latency and number of failures, (R)-ketamine only, (S)-ketamine had no effect on LH | IP | (R)-ketamine, but not (S)-ketamine has an AD effect in a rat LH model. |
| (Yang et al., 2018) | Mouse | C57BL/6 | M | 10<br>*(R)-ketamine* | CSDS | 1d (TST)<br>1d (FST)<br>7d (SPT) | LMT<br>TST<br>FST<br>SPT | • LMT: = Locomotion<br>• TST: ↓ Immobility<br>• FST: ↓ Immobility<br>• SPT: ↑ Sucrose preference | IP | |

| Citation | Animal | Strain | M/F | Dose in mg/kg<br>*Enantiomer* | Stress Model | Time of Testing (after last injection) | Tests | Behavioural Responses, time (dose) | Injection Method | Special Notes/Considerations |
|---|---|---|---|---|---|---|---|---|---|---|
| (Yang et al., 2018) | Mouse | C57BL/6 | M | 10<br>*(S)-ketamine* | CSDS | 1d (TST)<br>1d (FST)<br>7d (SPT) | LMT<br>TST<br>FST<br>SPT | • LMT: = Locomotion<br>• TST: ↓ Immobility<br>• FST: ↓ Immobility<br>• SPT: ↑ Sucrose preference | IP | |
| (Zanos et al., 2016) | Mouse | C57BL/6J | M/F | 1, 3, 10, 30, 50 (FST)<br>10 (LH)<br>*(R,S)-ketamine* | CSDS | 1h, 24h (FST)<br>1d (LH) | FST<br>LH | • FST: ↓ Immobility time, 1h (10, 30) (M/F grouped)<br>• FST: ↓ Immobility time, 24h (10) (M/F grouped)<br>• LH: ↓ Number of escape failures<br>For males at 24 hours, only (10) reduced immobility in the FST, but both (3) and (10) reduced immobility in females.<br>• Greater antidepressant potency in female mice | IP | Deuterated ketamine (which only affects its metabolism into HNK) did not induce AD effects in the FST or LH at 24h, suggesting a role of (2S,6S;2R,6R)-HNK in the sustained effects.<br>Estrus cycle not taken into account. |
| (Zanos et al., 2016) | Mouse | C57BL/6J | M/F | 1, 3, 10, 30 (FST, NSF)<br>1, 5, 25 (LH)<br>*(R)-ketamine* | CSDS | 1h, 24h (FST)<br>30min, 60min (NSF)<br>1d (LH) | FST<br>NSF<br>LH | • FST: ↓ Immobility, 1h (3, 10, 30)<br>• FST: ↓ Immobility, 24h (10, 30)<br>• LH: ↓ Number of escape failures (5, 25)<br>• NSF: ↓ Latency | IP | Greater potency of (R)-ketamine in the FST, NSF, and LH.<br>Estrus cycle not taken into account. |
| (Zanos et al., 2016) | Mouse | C57BL/6J | M/F | 1, 3, 10, 30<br>*(S)-ketamine* | CSDS | 1h, 24h (FST)<br>30min, 60min (NSF)<br>1d (LH) | FST<br>NSF<br>LH | • FST: ↓ Immobility, 1h (30)<br>• FST: = Immobility, 24h<br>• LH: ↓ Number of escape failures (25) | IP | Greater potency of (R)-ketamine in the FST, NSF, and LH.<br>Estrus cycle not taken into account. |
| (Zanos et al., 2016) | Mouse | C57BL/6J | M/F | 3, 10 (FST)<br>10 (LH)<br>*(2R,6R)-HNK*<br>*(2S, 6S)-HNK* | CSDS | 24h (FST)<br>1d (LH) | FST<br>LH | *(2R,6R)-HNK*<br>• FST: ↓ Immobility (10)<br>• LH: ↓ Number of escape failures<br>*(2S,6S)-HNK*<br>• FST: = Immobility<br>• LH: = Number of escape failures | IP | (2R,6R)-HNK more potent than (2S,6S)-HNK.<br>(2R,6R)-HNK lacks ketamine's side effects.<br>Estrus cycle not taken into account. |

**List of Abbreviations**

| Behavioural Test Abbreviations | Stress Model Abbreviations | Other Abbreviations |
|---|---|---|
| CPA: Conditioned Place Aversion | CMS: Chronic Mild Stress | (m)(dl)PFC: (medial)(dorsolateral) Prefrontal Cortex |
| CPP: Conditioned Place Preference | CSDS: Chronic Social Defeat Stress | D1: Diestrus |
| EPM: Elevated Plus Maze | CSIS: Chronic Social Isolation Stress | HC: Hippocampus |
| FST: Forced Swim Test | CUS: Chronic Unpredictable Stress | IP: Intraperitoneal |
| HBT: Holeboard Test | ES: Emotional/Psychological Stress | IV: Intravenous |
| KC: Ketamine Challenge | IES: Inescapable Shock | NAcC: Nucleus Accumbens Core |
| LDB: Light-Dark Box | LPS: Lipopolysaccharide Inflammation | NAcSh: Nucleus Accumbens Shell |
| LMT: Locomotor test | SDS: Social Defeat Stress | NS: Not Specified |
| MBT: Marble Burying Test | US: Uncontrollable Stress | PE: Proestrus |
| NSF: Novelty Suppressed Feeding | | |
| OFLA: Open Field Locomotor Activity | | |
| OFT: Open Field Test | | |
| PPI: Pre-Pulse Inhibition | | |
| SIT: Social Interaction Test | | |
| SplT: Splash Test | | |
| SPT: Sucrose Preference Test | | |
| TST: Tail Suspension Test | | |

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