Supplementary Table S2. Molecular Effects of Ketamine in Preclinical Models

Citation	Animal	Strain	M/F	Dose in mg/kg *Enantiomer*	Stress Model	Time of Testing (after last injection)	Molecular Changes, time (dose)	Injection Method	Tissue Collection Method	Special Notes/Considerations
(Autry et al., 2011)	Mouse	C57BL/6	M	3 *(R,S)-ketamine*	Naïve	30min, 24h	*mPFC* • ↑ BDNF, 30min • = GluR1 • = p-p70S6K • = p-mTOR • = p-eEF2 *HC* • ↑ BDNF, 30min • ↑ ARC, 30min • ↓ p-eEF2, 30 min • = p-mTOR	IP	Whole Tissue	↑ BDNF protein, but not mRNA (regulation at the level of translation).
(Carrier and Kabbaj, 2013)	Rat	Sprague Dawley	M	2.5, 5 *(R,S)-ketamine*	Naïve	30min	Whole Tissue *mPFC* • = total mTOR • = p-mTOR *HC* • ↓ p-eEF2 (5) Synaptoneurosomes *mPFC* • ↑ p-mTOR (5) • Synaptoneurosomes with ↑ p-mTOR were also highly concentrated with PSD-95	IP	Synaptoneurosomes Whole Tissue	
(Carrier and Kabbaj, 2013)	Rat	Sprague Dawley	F	2.5, 5 *(R,S)-ketamine*	Naïve	30min	*Whole Tissue* *mPFC* • = total mTOR • = p-mTOR *HC* • = p-eEF2 Synaptoneurosomes *mPFC* • ↑ p-mTOR (5) • Synaptoneurosomes with ↑ p-mTOR were also highly concentrated with PSD-95	IP	Synaptoneurosomes Whole Tissue	No increase in activated mTOR irt (2.5), suggesting that the increased sensitivity to ketamine is not due to mTOR/eEF2 activation in the PFC of female rat. Increased sensitivity lost when female rats are OVX. Estrus cycle not taken into account.
(Chang et al., 2018)	Mouse	C57BL/6J	M/F	3, 10 *(R)-ketamine*	LPS	10, 30, 60, 120, 180	No differences between M/F in terms of acute pharmokinetic profiles.	IP	Plasma Brain (Whole Tissue)	Estrus cycle not taken into account.

Citation	Animal	Strain	M/F	Dose in mg/kg *Enantiomer*	Stress Model	Time of Testing (after last injection)	Molecular Changes, time (dose)	Injection Method	Tissue Collection Method	Special Notes/Considerations
(Dossat et al., 2018)	Mouse	C57BL/6J	M	1.5, 3 *(R,S)-ketamine*	Naïve	1h	*PFC* • = p-CaMKIIα • ↑ p-GluR1 (3) • ↑ BDNF (3) • = p-MAPK • ↑ p-Akt (3) • ↑ p-GSK3β (1.5, 3) • ↑ p-mTOR (3) *HC* • ↑ CaMKIIα (3) • ↑ p-GluR1 (3) • ↑ BDNF (3) • ↑ p-MAPK (3) • ↑ p-Akt (3) • ↑ p-GSK3β (1.5, 3) • ↑ p-mTOR (3)	IP	Whole Tissue	
(Dossat et al., 2018)	Mouse	C57BL/6J	F	1.5, 3 *(R,S)-ketamine*	Naïve	1h	*PFC* • = CaMKIIα • ↑ GluR1 (PE: 1.5, 3) • ↑ BDNF (PE: 3) • = p-MAPK • ↑ p-Akt (PE: 1.5, 3) • ↑ p-GSK3β (PE: 3) • ↑ p-mTOR (D1: 3) *HC* • ↑ CaMKIIα (PE: 1.5, 3) • ↑ p-GluR1 (PE: 3) • ↑ BDNF (D1: 3) • ↑ p-MAPK (D1: 1.5, 3; PE: 3) • ↑ p-Akt (PE: 1.5, 3) • ↑ p-GSK3β (D1: 3; PE: 3) • ↑ p-mTOR (PE: 3)	IP	Whole Tissue	Giving an ERα/β agonist was sufficient to increase behavioural sensitivity in D1 females. 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	10 *(R,S)-ketamine*	Naïve	30min, 24h	*PFC* • = Asp • = 5-HIAA/5-HT *HC* • ↓ Glu, 30min • = 5-HIAA/5-HT	IP	Whole Tissue	
(Franceschelli et al., 2015)	Mouse	C57BL/6J	F	10 *(R,S)-ketamine*	Naïve	30min, 24h	*PFC* • ↑ Asp, 30min • ↓ 5-HIAA/5-HT, 24h *HC* • = Glu • ↓ 5-HIAA/5-HT, 24h	IP	Whole Tissue	Estrus cycle not taken into account.

Citation	Animal	Strain	M/F	Dose in mg/kg *Enantiomer*	Stress Model	Time of Testing (after last injection)	Molecular Changes, time (dose)	Injection Method	Tissue Collection Method	Special Notes/Considerations
(Garcia et al., 2008a)	Rat	Wistar	M	5, 10, 15; 14d Once Daily *(R,S)-ketamine*	Naïve	Day 14	*HC* • = BDNF	IP	Whole Tissue	
(Garcia et al., 2008b)	Rat	Wistar	M	5, 10, 15 *(R,S)-ketamine*	Naïve	60min	*HC* • ↑ BDNF (15)	IP	Whole Tissue	
(Garcia et al., 2009)	Rat	Wistar	M	15; acute *(R,S)-ketamine*	Naïve	NS	• = ACTH • = Corticosterone *HC* • = BDNF	IP	Whole Tissue	
(Garcia et al., 2009)	Rat	Wistar	M	15; 7d Once Daily *(R,S)-ketamine*	Naïve	NS	• = ACTH • = Corticosterone *HC* • = BDNF	IP	Whole Tissue	Larger differences in chronic than acute ketamine administration.
(Garcia et al., 2009)	Rat	Wistar	M	15; acute *(R,S)-ketamine*	CMS	NS	• ↓ ACTH • ↓ Corticosterone *HC* • = BDNF	IP	Whole Tissue	
(Garcia et al., 2009)	Rat	Wistar	M	15; 7d Once Daily *(R,S)-ketamine*	CMS	NS	• ↓ ACTH (more than acute) • ↓ Corticosterone (more than acute) *HC* • = BDNF	IP	Whole Tissue	Larger differences in chronic than acute ketamine administration.
(Guo et al., 2016)	Rat	Sprague Dawley	M/F	6-14; 9d (Once daily) *(R,S)-ketamine*	Naïve	0d, 1d, 3d, 5d, 7d, 9d, 10, 12d, 14d, 16d	"Metabolic trajectory fluctuation of the female rats was relatively larger than that of male rats." "Different metabolites between ketamine-induced male and female rats."	NS	Urine (Metabolics)	Estrus cycle not taken into account.
(Li et al., 2010)	Rat	Sprague Dawley	M	10 *(R,S)-ketamine*	IES	30min, 1h, 2h, 6h, 72h	*PFC* • ↑ p-mTOR, 30min-1h • ↑ p-4E-BP, 30min-1h • ↑ p-p70S6K, 30min-1h • ↑ p-ERK, 30min-1h • ↑ p-Akt, 30min-1h • ↑ ARC, 1h-2h • ↑ Synapsin-1, 2h-72h • ↑ PSD-95, 2h-72h • ↑ GluR1, 2h-72h	IP	Synaptoneurosomes	Pharmacological inhibition of ERK or Akt blocked ketamine-induction of phosphorylated 4E-BP, mTOR, and p70S6K. Rapamycin blocked ketamine-induction of PSD-95, GluR1, and Synapsin-1.
(Li et al., 2011)	Rat	Sprague Dawley	M	10 *(R,S)-ketamine*	CUS	8d	*PFC* • ↑ Synapsin-1, PSD-95, GluR1	IP	Synaptoneurosomes	

Citation	Animal	Strain	M/F	Dose in mg/kg *Enantiomer*	Stress Model	Time of Testing (after last injection)	Molecular Changes, time (dose)	Injection Method	Tissue Collection Method	Special Notes/Considerations
(Nishitani et al., 2014)	Rat	Wistar/ST	M	1, 5, 25 *(R,S)-ketamine*	Naïve	Every 10min for 60min	*mPFC* • ↑ 5-HT, 10min-40min (5) • ↑ 5-HT, 10min-50min (25)	SC	In vivo measurement via cannulation	Increase in 5-HT in the mPFC was through AMPAR activation. NBQX attenuated the increase in ketamine-induced 5-HT.
(Paul et al., 2014)	Rat	Wistar	M	40 *(R,S)-ketamine*	Naïve	30min, 60min, 240min	*PFC* • ↑ p-mTOR, 30min-60min • ↑ p-p70S6K, 30min-60min • = p-4E-BP • = p-ERK • = p-Akt	IP	Whole tissue	
(Paul et al., 2014)	Rat	Wistar	M	20 *(R,S)-NK*	Naïve	20min, 60min, 240min	*PFC* • ↑ p-mTOR, 20min-60min • ↑ p-p70S6K, 20min-60min • ↑ p-4E-BP, 60min • ↑ p-ERK, 20-60min • = p-Akt	IP	Whole Tissue	
(Paul et al., 2014)	Rat	Wistar	M	20 *(R,S)-HNK*	Naïve	20min, 60min, 240min	*PFC* • ↑ p-mTOR, 20min • ↑ p-p70S6K, 20min-60min • ↑ p-4E-BP, 20min-60min • = p-ERK • = p-Akt	IP	Whole Tissue	

Citation	Animal	Strain	M/F	Dose in mg/kg *Enantiomer*	Stress Model	Time of Testing (after last injection)	Molecular Changes, time (dose)	Injection Method	Tissue Collection Method	Special Notes/Considerations
(Saland and Kabbaj, 2018)	Rat	Sprague Dawley	M/F	2.5 *(R,S)-ketamine*	Naïve	NS	• Peak plasma concentrations of K/NK higher and established earlier in females than males. • Peak plasma concentrations of DNHK higher and established earlier in males than females. • NK higher in the PFC and HC in females • Distribution or permeability of NK into the brain is greater in females than males • Males have slower elimination or greater retention of ketamine in the brain. • Both K/NK concentrations were higher in the PFC than HC for females; roughly the same for males	IP	Plasma Whole Tissue (Brain)	Pharmacokinetic study. There were no sig differences in drug/metabolite localization due to stage of the estrus cycle, supporting a dynamic rather than kinetic influence.
(Saland et al., 2016)	Rat	Sprague Dawley	M	2.5; on days 4 and 6 (of 6) *(R,S)-ketamine*	Naïve	24h-7d Tested once daily	*HC* • = BDNF • = p-ERK • = p-Akt	IP	Whole Tissue	
(Saland et al., 2016)	Rat	Sprague Dawley	F	2.5; on days 4 and 6 (of 6) *(R,S)-ketamine*	Naïve	24h-7d Tested once daily	*HC* • ↑ BDNF, 24h • = p-ERK • = p-Akt	IP	Whole Tissue	Suggests that the increase in response of females to ketamine is not due to ERK/Akt activation in the HC. Differences could be due to organizational differences of E2/P4 w/in the HC. 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	1h after FST (3d)	*mPFC* • ↑ Synapsin-1 (5) • ↑ PSD-95 (5) • ↑ GluR1 (5)	NS	Synaptoneurosomes	

Citation	Animal	Strain	M/F	Dose in mg/kg *Enantiomer*	Stress Model	Time of Testing (after last injection)	Molecular Changes, time (dose)	Injection Method	Tissue Collection Method	Special Notes/Considerations
(Sarkar and Kabbaj, 2016)	Rat	Sprague Dawley	F	2.5, 5 *(R,S)-ketamine*	CSIS	1h after FST (3d)	*mPFC* • = Synapsin-1 • = PSD-95 • = GluR1	NS	Synaptoneurosomes	Females injected with ketamine during D1.
(Schoepfer et al., 2019)	Rat	Sprague Dawley	M	2.5, 5, 10; 10d Every other day *(R,S)-ketamine*	Naïve	Day 12	*NAc* • ↑ ΔFosB (2.5, 5, 10)	IP	Whole Tissue	No sex differences in protein expression within each dose level.
(Schoepfer et al., 2019)	Rat	Sprague Dawley	F	2.5, 5, 10; 10d Every other day *(R,S)-ketamine*	Naïve	Day 12	*NAc* • ↑ ΔFosB (2.5, 5, 10)	IP	Whole Tissue	ΔFosB expression was greater in females than in males. No sex differences in protein expression within each dose level. Estrus cycle not taken into account.
(Strong et al., 2017)	Rat	Sprague Dawley	M	2.5, 5; 1/wk for 7 wk *(R,S)-ketamine*	Naïve	2h after ketamine challenge (2wk)	*NAc* • ↑ ΔFosB (5) • ↑ CaMKIIα (5) • = p-CaMKIIα • ↑ BDNF (5) • ↑ GluR1 (5, trend)	IP	Whole Tissue	Increased expression of proteins associated with sensitization in males but not females.
(Strong et al., 2017)	Rat	Sprague Dawley	F	2.5, 5; 1/wk for 7 wk *(R,S)-ketamine*	Naïve	2h after ketamine challenge (2wk)	*NAc* • = ΔFosB • = CaMKIIα • = p-CaMKIIα • = BDNF • ↑ GluR1 (5)	IP	Whole Tissue	All females were tested in D1.
(Thelen et al., 2016)	Mouse	C57BL/6J	M	3, 5, 10; 21 d Once daily *(R,S)-ketamine*	Naïve	Day 22	*HC* • = Glu • = Asp • ↑ 5-HIAA (10) • ↑ 5-HIAA/5-HT (10) • ↑ Synapsin-1 (10) • ↑ SNARE-100 (10)	IP	Synaptoneurosomes	
(Thelen et al., 2016)	Mouse	C57BL/6J	F	3, 5, 10; 21 d Once daily *(R,S)-ketamine*	Naïve	Day 22	*HC* • ↓ Glu (10) • ↓ Asp (10) • = 5-HIAA • = 5-HIAA/5-HT • = Synapsin-1 • = SNARE-100	IP	Synaptoneurosomes	Estrus cycle not taken into account.

Citation	Animal	Strain	M/F	Dose in mg/kg *Enantiomer*	Stress Model	Time of Testing (after last injection)	Molecular Changes, time (dose)	Injection Method	Tissue Collection Method	Special Notes/Considerations
(Thelen et al., 2019)	Mouse	C57BL/6J	M	10 *(R,S)-ketamine*	Naïve	Every 10min for 60min (Glu) 0.5h, 4h, 24h, 3d, 7d (Proteins)	*mPFC* • ↑ Glu, 10min; burst • ↑ p-mTOR, 0.5h-24h • ↑ GluR1, 4h • ↑ GluR2, 4h-24h *HC* • = p-mTOR • ↑ GluR1, 4h	IP	Synaptoneurosomes	
(Thelen et al., 2019)	Mouse	C57BL/6J	F	10 *(R,S)-ketamine*	Naïve	Every 10min for 60min (Glu) 0.5h, 4h, 24h, 3d, 7d (Proteins)	*mPFC* • = Glu release • ↓ p-mTOR, 4h • = GluR1 • = GluR2 *HC* • = p-mTOR • = GluR1	IP	Synaptoneurosomes	Estrus cycle not taken into account.
(Tizabi et al., 2012)	Rat	Wistar-Kyoto (WKY)	F	0.5; 10d Once daily *(R,S)-ketamine*	Naïve	20h	*HC* • ↑ AMPAR densities • ↑ AMPAR/NMDAR ratio	IP	Whole Tissue	
(Tizabi et al., 2012)	Rat	Wistar	F	0.5; 10d Once daily *(R,S)-ketamine*	Naïve	20h	*HC* • = AMPAR densities • = AMPAR/NMDAR ratio	IP	Whole Tissue	
(Yang et al., 2015)	Mouse	C57BL/6	M	10 *(R)-ketamine* *(S)-ketamine*	SDS	7d	*mPFC* • ↑ BDNF • ↑ GluR1 *HC* • ↑ CA3/DG BDNF • ↑ GluR1 (R)-ketamine more potent on altering BDNF, but have similar effects on GluR1	IP	Whole Tissue	(R)-ketamine more potent than (S)-ketamine.
(Yang et al., 2018)	Mice	C57BL/6	M	10 *(R)-ketamine*	CSDS	30min	*PFC* • = p-mTOR • = p-p70S6K • = GluR1 • = BDNF • ↓ p-eEF2 • ↑ p-ERK • ↑ p-MEK *HC* • = CA3/DG p-mTOR • ↓ DG p-mTOR • = p-p70S6K • ↑ CA3/DG p-ERK • ↑ DG p-MEK	IP	Whole Tissue	ERK may play a role in the AD effects of (R)-ketamine, but not (S)-ketamine, in the CSDS model.

Citation	Animal	Strain	M/F	Dose in mg/kg *Enantiomer*	Stress Model	Time of Testing (after last injection)	Molecular Changes, time (dose)	Injection Method	Tissue Collection Method	Special Notes/Considerations
(Yang et al., 2018)	Mice	C57BL/6	M	10 *(S)-ketamine*	CSDS	30min	*PFC* • ↑ p-mTOR • ↑ p-p70S6K • = GluR1 • = BDNF • ↓ p-eEF2 • = p-ERK • = p-MEK *HC* • ↑ CA3/DG p-mTOR • = DG p-mTOR • = p-p70S6K • = CA3/DG p-ERK • = DG p-MEK	IP	Whole Tissue	mTOR may play a role in the AD effects of (S)-ketamine, but not (R)-ketamine, in the CSDS model.
(Zanos et al., 2016)	Mouse	C57BL/6J	M/F	10 *(R,S)-ketamine*	CSDS	1h, 24h	• Equivalent levels of ketamine and norketamine in males and females • 3x higher (2S,6S;2R,6R)-HNK in the brains of females than males Males: *PFC* • = p-mTOR • = p-eEF2 • = BDNF • = GluR1 • = GluR2 *HC* • = p-mTOR • ↓ p-eEF2, 1h, 24h • ↑ BDNF, 24h • ↑ GluR1, 24h • ↑ GluR2, 24h	IP	Synaptoneurosomes	Estrus cycle not taken into account.

Citation	Animal	Strain	M/F	Dose in mg/kg *Enantiomer*	Stress Model	Time of Testing (after last injection)	Molecular Changes, time (dose)	Injection Method	Tissue Collection Method	Special Notes/Considerations
(Zanos et al., 2016)	Mouse	C57BL/6J	M/F	10 *(2R,6R)-HNK* *(2S, 6S)-HNK*	CSDS	1h, 24h	*(2R,6R)-HNK* *PFC* • = p-mTOR • = p-eEF2 • = GluR1 • = GluR2 *HC* • = p-mTOR • ↓ p-eEF2, 1h, 24h • ↑ BDNF, 24h • ↑ GluR1, 24h • ↑ GluR2	IP	Synaptoneurosomes	(2R,6R)-HNK more potent than (2S,6S)-HNK. (2R,6R)-HNK does not inhibit NMDARs. (2R,6R)-HNK requires AMPARs for its antidepressant effects (abolished by NBQX). (2R,6R)-HNK lacks ketamine's side effects. Estrus cycle not taken into account.

List of Abbreviations

Stress Model Abbreviations	Other Abbreviations
CMS: Chronic Mild Stress	(m)(dl)PFC: (medial)(dorsolateral) Prefrontal Cortex
CSDS: Chronic Social Defeat Stress	D1: Diestrus
CSIS: Chronic Social Isolation Stress	HC: Hippocampus
CUS: Chronic Unpredictable Stress	IP: Intraperitoneal
ES: Emotional/Psychological Stress	IV: Intravenous
IES: Inescapable Shock	NAcC: Nucleus Accumbens Core
LPS: Lipopolysaccharide Inflammation	NAcSh: Nucleus Accumbens Shell
SDS: Social Defeat Stress	NS: Not Specified
US: Uncontrollable Stress	PE: Proestrus

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