

**Table S1:**

a) Subcellular localization and function of altered proteins isolated from **rat spleen lymphocytes** after 7-day treatment with **morphine, LYS739** and **LYS744** (**3 mg/kg**) identified by label-free quantification (MaxLFQ).

Accession number	Protein name	Gene	Change (fold)	p value	Subcellular localization	Molecular functions and biological processes- keywords
<b>Lymphocytes -MORPHINE – 3 mg/kg, 7 days:</b>						
<i>UP-regulated</i>						
1-Q63633	Solute carrier family 12 member 5	<b>Slc12a5</b>	↑1.1	0.0008	Cell membrane	Ion transport
2-Q05764	Beta-adducin	<b>Add2</b>	↑4.0	0.0076	Cell membrane, cytoskeleton	Actin filament bundle assembly
3-Q9QWN8	Spectrin beta chain, non-erythrocytic 2	<b>Sptbn2</b>	↑3.9	0.0280	Cytoplasm, cytoskeleton	Actin filament capping
4-Q6AZ54	Hemogen	<b>Hemgn</b>	↑3.4	<0.0001	Nucleus	Cell differentiation
5-P40615	H/ACA ribonucleoprotein complex subunit 4	<b>Dkc1</b>	↑2.6	0.0095	Nucleus	RNA processing
6-Q5PPN5	Tubulin polymerization-promoting protein family member 3	<b>Tppp3</b>	↑2.6	0.0189	Cytoplasm, cytoskeleton	Microtubule polymerization
7-P35465	Serine/threonine-protein kinase PAK 1	<b>Pak1</b>	↑2.4	0.0255	Cytoplasm, cell membrane, nucleus	Apoptosis, exocytosis
8-P24135	1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2	<b>Plcg2</b>	↑2.4	<0.0001	Cytoplasm, cell membrane	Signal transduction, lipid metabolism
9-A0A140UHX6	Spectrin beta chain	<b>Sptbn2</b>	↑2.0	0.0199	Cytoplasm, cytoskeleton	Actin filament capping
10-Q99JD4	CLIP-associating protein 2	<b>Clasp2</b>	↑2.0	0.0127	Cell membrane, cytoplasm, GA*	Cell cycle
11-D3Z9Z0	Ankyrin-1	<b>Ank1</b>	↑2.0	0.0131	Cytoskeleton, ER**, nucleus	Vesicle-mediated transport
12-B0BNN3	Carbonic anhydrase 1	<b>Ca1</b>	↑2.0	<0.0001	Cytoplasm	Reversible hydration of carbon dioxide
<i>Down-regulated</i>						
1-P30337	N-chimaerin	<b>Chn1</b>	↓12.3	0.0386	Cytoplasm	Signal transduction, neurogenesis
2-Q4QRB4	Tubulin beta-3 chain	<b>Tubb3</b>	↓5.1	0.0399	Cytoplasm, cytoskeleton	Cytoskeleton organization
3-P11275	Calcium/calmodulin-dependent protein kinase type II subunit alpha	<b>Camk2a</b>	↓4.7	0.0389	Cell junction, synapse	Calcium ion transport, protein phosphorylation
4-P31596	Excitatory amino acid transporter 2	<b>Slc1a2</b>	↓4.3	0.0049	Cell membrane	Amino-acid transport
5-P0C170	Histone H2A type 1-E	<b>N/A</b>	↓3.7	0.0073	Nucleus	DNA processing
6-D4A7H9	Charged multivesicular body protein 7	<b>Chmp7</b>	↓2.9	0.0360	Cytoplasm, endosome, nucleus	Transport, nucleus organization
7-Q62950	Dihydropyrimidinase-related protein 1	<b>Crmp1</b>	↓2.8	0.0252	Cytoplasm, cytoskeleton	Cytoskeleton organization, axon guidance
8-P31000	Vimentin	<b>Vim</b>	↓2.8	0.0016	Cell membrane, cytoskeleton, nucleus	Ageing, intermediate filament organization

9-P07151	Beta-2-microglobulin	<b>B2m</b>	↓2.7	0.0017	Secreted	Immunity
10-P63312	Thymosin beta-10	<b>Tmsb10</b>	↓2.7	0.0134	Cytoplasm, cytoskeleton	Cytoskeleton organization
11-P10960	Sulfated glycoprotein 1	<b>Psap</b>	↓2.7	0.0171	Lysosome	Glycosphingolipid metabolism, signal transduction
12-P09495	Tropomyosin alpha-4 chain	<b>Tpm4</b>	↓2.3	0.0242	Cytoplasm, cytoskeleton	Actin filament organization
13-D4AD33	RNA guanine-7 methyltransferase-activating subunit	<b>Ramac</b>	↓2.2	0.0014	Nucleus	RNA processing
14-Q64122	Myosin regulatory light polypeptide 9	<b>MyI9</b>	↓2.0	0.0055	Cytoplasm, cytoskeleton	Motor protein, cell locomotion
15-Q5BK20	Jupiter microtubule associated homolog 2	<b>Jpt2</b>	↓2.0	0.0033	Cytoplasm, nucleus	Protein phosphorylation

## Lymphocytes -LYS739 – 3 mg/kg, 7 days

### UP-regulated

1-D3ZSY4	Eosinophil peroxidase	<b>Epx</b>	↑2.7	0.0002	Secreted	Heme binding, oxidative stress response
2-P13832	Myosin regulatory light chain RLC-A	<b>Rlc-a</b>	↑2.5	0.0031	Cytoplasm, cytoskeleton	Motor protein, regulation of cell shape
3-P40615	H/ACA ribonucleoprotein complex subunit 4	<b>Dkc1</b>	↑2.2	0.0149	Nucleus	RNA processing
4-Q4FZX5	Methionine-R-sulfoxide reductase B2, mitochondrial	<b>Msrb2</b>	↑2.2	0.0233	Mitochondrion	Protein repair, oxidative stress response
5-Q925G1	Hepatoma-derived growth factor-related protein 2	<b>Hdgfrp2</b>	↑2.0	0.0184	Nucleus	Regulation of cell growth, RNA processing

### Down-regulated

1-P31596	Excitatory amino acid transporter 2	<b>Slc1a2</b>	↓4.0	0.0289	Cell membrane	Amino-acid transport
2-P09812	Glycogen phosphorylase, muscle form	<b>Pygm</b>	↓4.0	0.0043	ER, cytoplasm	Glycogen metabolism
3-D4A206	Treacle ribosome biogenesis factor 1	<b>Tcof1</b>	↓3.0	0.0028	Cytoplasm, nucleus	Regulation of translation
4-P09951	Synapsin-1	<b>Syn1</b>	↓2.7	0.0323	GA	Neurotransmitter release cycle
5-P02401	60S acidic ribosomal protein P2	<b>Rplp2</b>	↓2.6	<0.0001	Cytoplasm, ribosome	Regulation of translation
6-A0A0G2K2M9	Serine/arginine repetitive matrix 2	<b>Srrm2</b>	↓2.6	0.0086	Nucleus	RNA processing
7-P08081	Clathrin light chain A	<b>Clta</b>	↓2.4	0.0016	Cytoplasm, cytoskeleton, cell membrane	Cell cycle, protein transport
8-D4A4P3	Complex I-B12	<b>Ndufb3</b>	↓2.3	0.0079	Mitochondrion	Electron transport chain
9-Q66HF8	Aldehyde dehydrogenase X, mitochondrial	<b>Aldh1b1</b>	↓2.2	0.0222	Mitochondrion	Ethanol oxidation, lipid peroxidation
10-P07151	Beta-2-microglobulin	<b>B2m</b>	↓2.2	0.0034	Secreted	Immunity
11-P09495	Tropomyosin alpha-4 chain	<b>Tpm4</b>	↓2.1	0.0307	Cytoplasm, cytoskeleton	Actin filament organization
12-Q3LRZ1	CREB-regulated transcription coactivator 2	<b>Crtc2</b>	↓2.0	0.0175	Cytoplasm, nucleus	Regulation of transcription
13-A1L1K4	CDC42 small effector protein 2	<b>Cdc42se2</b>	↓2.0	0.0425	Cell membrane, cytoplasm, cytoskeleton	Cell shape, signal transduction
14-P10960	Sulfated glycoprotein 1	<b>Psap</b>	↓2.0	0.0183	Lysosome	Glycosphingolipid metabolism, signal transduction

15-F1LNI5	Protein phosphatase 1G	<b>Ppm1g</b>	↓2.0	0.0450	Cytoplasm, cell membrane	Cell cycle
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## Lymphocytes -LYS744 – 3 mg/kg, 7 days

### UP-regulated

1-E9PU01	DNA helicase	<b>Chd4</b>	↑3.8	0.0411	Nucleus, cytoplasm	Chromatin organization
2-P14046	Alpha-1-inhibitor 3	<b>A1i3</b>	↑3.5	0.0178	Secreted	Protease inhibitor
3-P97710	Tyrosine-protein phosphatase non-receptor type substrate 1	<b>Sirpa</b>	↑3.3	0.0038	Cell membrane	Cell-matrix adhesion, cytoskeleton organization
4-D3ZKT0	Phosphatidate cytidyltransferase, mitochondrial	<b>Tamm41</b>	↑2.7	0.0454	Cell membrane, mitochondrion	Lipid metabolism
5-Q64548	Reticulon-1	<b>Rtn1</b>	↑2.6	0.0339	ER membrane, GA membrane	Regulation of amyloid-beta formation
6-D3ZFD0	Unconventional myosin-XVIIIa	<b>Myo18a</b>	↑2.4	0.0043	Cytoplasm, GA	Motor protein, Golgi organization
7-A0A140UHX6	Spectrin beta chain	<b>Sptb</b>	↑2.4	0.0076	Cytoplasm, cytoskeleton	Actin capping
8-D3Z9Z0	Ankyrin 1	<b>Ank1</b>	↑2.4	0.0065	Cytoskeleton, cell membrane, ER, nucleus	ER to Golgi vesicle-mediated transport
9-Q63355	Unconventional myosin-Ic	<b>Myo1c</b>	↑2.4	0.0190	Cell membrane, cytoplasm	Protein transport, motor protein
10-Q9WU82	Catenin beta-1	<b>Cttnb1</b>	↑2.4	0.0353	Cell membrane, cytoplasm, nucleus	Cell adhesion, neurogenesis
11-F1LP64	E3 ubiquitin-protein ligase TRIP12	<b>Trip12</b>	↑2.3	0.0010	Nucleus	DNA processing
12-B2RYU7	Cbx5 protein	<b>Cbx5</b>	↑2.3	0.0019	Nucleus	Regulation of transcription
13-Q66HG8	Protein Red	<b>Ik</b>	↑2.3	0.0136	Cytoplasm, cytoskeleton, nucleus	RNA processing
14-P02688	Myelin basic protein	<b>Mbp</b>	↑2.3	0.0004	Cell membrane	Aging, myelination
15-D4ABI7	Very-long-chain (3R)-3-hydroxyacyl-CoA dehydratase	<b>Hcd3</b>	↑2.3	0.0058	ER, cell membrane	Lipid metabolism
16-P09951	Synapsin-1	<b>Syn1</b>	↑2.3	0.0291	GA	Neurotransmitter release cycle
17-B2GUY4	Dematin actin-binding protein	<b>Dmtn</b>	↑2.3	0.0098	Cytoplasm, cytoskeleton, cell membrane	Actin cytoskeleton organization
18-Q5RKH0	Putative oxidoreductase GLYR1	<b>Glyr1</b>	↑2.2	0.0071	Nucleus	Regulation of transcription
19-Q9QYF3	Unconventional myosin-Va	<b>Myo5a</b>	↑2.2	0.0104	Cytoplasm, cytoskeleton, GA, ER, endosome	Actin filament organization, protein transport
20-O35274	Neurabin-2	<b>Ppp1r9b</b>	↑2.2	0.0164	Cell membrane, cytoplasm, nucleus	Actin filament organization, neurogenesis
21-Q6P9V9	Tubulin alpha-1B chain	<b>Tuba1b</b>	↑2.2	0.0329	Cytoplasm, cytoskeleton	Cytoskeleton organization
22-Q5XIB5	Coiled-coil domain-containing protein 86	<b>Ccdc86</b>	↑2.2	0.0002	Nucleus	Citrullinated by PADI4
23-P22985	Xanthine dehydrogenase/oxidase	<b>Xdh</b>	↑2.2	0.0496	Cytoplasm, peroxisome, secreted	Purine degradation, aging
24-Q63356	Unconventional myosin-Ie	<b>Myo1e</b>	↑2.1	0.0028	Cytoplasmic vesicle, cytoskeleton	Actin filament organization, endocytosis
25-P13832	Myosin regulatory light chain RLC-A	<b>Rlc-a</b>	↑2.0	0.0116	Cytoplasm, cytoskeleton	Regulation of cell shape, motor protein
26-P55009	Allograft inflammatory factor 1	<b>Aif1</b>	↑2.0	0.0115	Cell membrane, cytoplasm, cytoskeleton	Actin filament polymerization, inflammatory response
27-B2RYI2	Signal recognition particle subunit SRP68	<b>Srp68</b>	↑2.0	0.0406	Cytoplasm	Protein targeting to the rough ER membrane
28-D3ZSY4	Eosinophil peroxidase	<b>Epx</b>	↑2.0	0.0002	Secreted	Neutrophil degranulation, oxidative stress response

29-Q6AYA2	VRK serine/threonine kinase 1	<b>Vrk1</b>	↑2.0	0.0013	Cytoplasm, nucleus, GA	Nuclear envelope breakdown, Golgi disassembly
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**Down-regulated**

1-A0A0G2JSV6	Globin c2	<b>Hba-a2</b>	↓11.6	0.0052	Cytoplasm, secreted	Oxygen transport
2-P13596	Neural cell adhesion molecule 1	<b>Ncam1</b>	↓4.5	0.0148	Cell membrane	Cell adhesion, aging
3-Q05175	Brain acid soluble protein 1	<b>Basp1</b>	↓4.5	0.0028	Cell membrane	Regulation of transcription
4-P63219	Guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-5	<b>Gng5</b>	↓3.3	0.0266	Cell membrane	Signal transduction
5-Q5BK20	Jupiter microtubule associated homolog 2	<b>Jpt2</b>	↓3.1	<0.0001	Cytoplasm, nucleus	Protein phosphorylation
6-D4AD33	RNA guanine-7 methyltransferase-activating subunit	<b>Ramac</b>	↓2.7	<0.0001	Nucleus	RNA processing
7-Q6IN36	WAS/WASL-interacting protein family member 1	<b>Wipf1</b>	↓2.4	0.0086	Cytoplasm, cytoskeleton	Actin cytoskeleton organization
8-D4A7H9	Charged multivesicular body protein 7	<b>Chmp7</b>	↓2.4	0.0361	Cytoplasm, endosome, nucleus	Transport, nucleus organization
9-Q62806	Zinc finger protein 148	<b>Znf148</b>	↓2.4	0.0009	Nucleus	Regulation of transcription
10-Q03344	ATPase inhibitor, mitochondrial	<b>Atpif1</b>	↓2.3	0.0003	Mitochondrion	Regulation of ATP metabolic process
11-P18291	Granzyme B	<b>Gzmb</b>	↓2.2	0.0018	Lysosome, secreted	Apoptosis
12-Q792Q4	Cysteine-rich PDZ-binding protein	<b>Cript</b>	↓2.2	0.0135	Cytoplasm, cell junction	Protein localization
13-A0A0G2K2M9	Serine/arginine repetitive matrix 2	<b>Srrm2</b>	↓2.2	0.0004	Nucleus	RNA processing
14-O08769	Cyclin-dependent kinase inhibitor 1B	<b>Cdkn1b</b>	↓2.1	0.0203	Cytoplasm, nucleus, endosome	Apoptosis, response to drug
15-M0R9Z5	Interferon regulatory factor 2-binding protein 2	<b>Irf2bp2</b>	↓2.1	0.0174	Nucleus	Regulation of transcription
16-G3V7E3	Granzyme A	<b>Gzma</b>	↓2.0	<0.0001	Nucleus	Apoptosis

**b) Subcellular localization and function of altered proteins isolated from rat brain cortex after 7-day treatment with morphine, LYS739 and LYS744 (3 mg/kg) identified by label-free quantification (MaxLFQ).**

Accession number	Protein name	Gene	Change (fold)	p value	Subcellular localization	Molecular functions and biological processes- keywords
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**CORTEX -MORPHINE – 3 mg/kg, 7 days**

**UP-regulated**

1-D3Z8E0	Ribosomal protein S6 kinase	<b>Rps6ka3</b>	↑2.7	0.0074	Cytoplasm, nucleus, ribosome	Signal transduction, apoptosis
2-M0R9Q1	RNA-binding motif protein 14	<b>Rbm14</b>	↑2.7	0.009	Cytoplasm, nucleus	Signal transduction, immunity

3-D3ZKT0	Phosphatidate cytidyltransferase, mitochondrial	<b>Tamm41</b>	↑2.1	0.0043	Cell membrane, mitochondrion	Lipid metabolism
4-Q99P82	Claudin-11	<b>Cldn11</b>	↑2.1	0.0004	Cell membrane	Cell adhesion
5-D3ZQ18	NCCRP1, F-box-associated domain-containing	<b>Nccrp1</b>	↑2.1	0.0129	Cytoplasm, nucleus	Protein ubiquitination

### Down-regulated

1-A0A0G2JSV6	Globin c2	<b>Hba-a2</b>	↓13.6	0.0150	Cytoplasm, secreted	Oxygen transport
2-P50116	Protein S100-A9	<b>S100a9</b>	↓3.7	0.0273	Cell membrane, cytoplasm, secreted	Actin cytoskeleton organization, apoptosis, immunity
3-B2RZ74	U1 small nuclear ribonucleoprotein 70 kDa	<b>Snrnp70</b>	↓3.5	0.0002	Cytoplasm, nucleus	RNA processing
4-D3ZQE8	Exportin 5	<b>Xpo5</b>	↓2.4	0.0215	Cytoplasm	Protein export
5-P02625	Parvalbumin alpha	<b>Pvalb</b>	↓2.4	0.0016	Cytoplasm, nucleus	Calcium-binding protein
6-Q9JID1	Programmed cell death protein 4	<b>Pdcd4</b>	↓2.3	0.0401	Cytoplasm, nucleus	Apoptosis
7-Q4KLZ3	DAZ-associated protein 1	<b>Dazap1</b>	↓2.3	0.0058	Cytoplasm, nucleus	RNA processing
8-Q63910	Alpha globin	<b>Hba-a3</b>	↓2.2	0.0021	Cytoplasm, secreted	Oxygen transport
9-E9PU28	Inosine-5-monophosphate dehydrogenase 2	<b>Impdh2</b>	↓2.2	0.0017	Cytoplasm, nucleus	Purine biosynthesis, RNA/DNA metabolism
10-Q3B8Q1	Nucleolar RNA helicase 2	<b>Ddx21</b>	↓2.2	0.0068	Cytoplasm, nucleus, mitochondrion	Immunity, RNA processing

## CORTEX -LYS739 – 3 mg/kg, 7 days

### UP-regulated

1-C0JPT7	Filamin A	<b>Flna</b>	↑3.5	0.0427	Cell membrane, cytoplasm, nucleus, GA	Actin cytoskeleton organization
2-D3ZQ18	NCCRP1, F-box-associated domain-containing	<b>Nccrp1</b>	↑3.0	0.0033	Cytoplasm	Protein ubiquitination
3-A0A0G2JT64	Aldo-keto reductase family 1, member B8	<b>Akr1b10</b>	↑2.9	0.0038	Cytoplasm, mitochondrion	Estrogen biosynthesis
4-D3ZX38	Prefoldin 1	<b>Pfdn1</b>	↑2.4	0.0015	Cytoplasm	Protein folding, actin cytoskeleton organization
5-A0A0G2JYU6	Formin-like 1	<b>Fmn1</b>	↑2.3	0.0337	Cell membrane, cytoplasm	Actin cytoskeleton organization
6-D3ZKT0	Phosphatidate cytidyltransferase, mitochondrial	<b>Tamm41</b>	↑2.1	0.0059	Cell membrane, mitochondrion	Lipid metabolism
7-B4F7A1	Complex III assembly factor LYRM7	<b>Lym7</b>	↑2.0	0.0040	Mitochondrion	Chaperone

### Down-regulated

1-P50116	Protein S100-A9	<b>S100a9</b>	↓10.5	0.0176	Cell membrane, cytoplasm, secreted	Actin cytoskeleton organization, apoptosis, immunity
2-Q00438	Polypyrimidine tract-binding protein 1	<b>Ptbp1</b>	↓8.4	0.0078	Nucleus	RNA processing, neurogenesis
3-B2RZ74	U1 small nuclear ribonucleoprotein 70 kDa	<b>Snrnp70</b>	↓6.5	0.0002	Cytoplasm, nucleus	RNA processing

4-D4ABT8	Heterogeneous nuclear ribonucleoprotein U-like 2	<b>Hnrnpul2</b>	↓5.4	0.0043	Nucleus	RNA binding
5-G3V7Q7	IQ motif-containing GTPase-activating protein 1	<b>Iqgap1</b>	↓5.2	0.0052	Cell membrane, cytoplasm, nucleus	Actin cytoskeleton organization, cell migration
6-F1LRS8	CD2-associated protein	<b>Cd2ap</b>	↓4.7	0.0015	Cytoplasm, cytoskeleton	Actin cytoskeleton organization, cell cycle
7-Q62780	Probable ATP-dependent RNA helicase DDX46	<b>Ddx46</b>	↓4.2	0.0310	Cell membrane, nucleus	RNA processing
8-Q5M860	Rho GDP dissociation inhibitor beta	<b>Arhgdib</b>	↓3.7	0.0136	Cell membrane, cytoplasm	Signal transduction
9-B1WC49	Api5 protein	<b>Api5</b>	↓3.2	0.0032	Nucleus	Apoptosis
10-Q3B8Q1	Nucleolar RNA helicase 2	<b>Ddx21</b>	↓3.2	0.0030	Cytoplasm, nucleus, mitochondrion	Immunity, RNA processing
11-G3V7T6	Splicing factor 3b, subunit 1	<b>Sf3b1</b>	↓2.2	0.0061	Nucleus	RNA processing
12-Q63797	Proteasome activator complex subunit 1	<b>Psme1</b>	↓2.0	0.0224	Cytoplasm, nucleus	Antigen processing, cell cycle
13-B5DES0	Small nuclear ribonucleoprotein Sm D2	<b>Snrpd2</b>	↓2.0	0.0213	Cytoplasm, nucleus	RNA processing

## CORTEX -LYS744 – 3 mg/kg, 7 days

### UP-regulated

1-C0JPT7	Filamin A	<b>Flna</b>	↑3.9	0.0099	Cell membrane, cytoplasm, nucleus, GA	Actin cytoskeleton organization
2-Q4V8E4	Cilia- and flagella-associated protein 36	<b>Cfap36</b>	↑3.0	0.0037	Cytoplasm, nucleus	Protein N-terminus binding
3-D3Z8E0	Ribosomal protein S6 kinase	<b>Rps6ka3</b>	↑2.9	0.0017	Cytoplasm, nucleus, ribosome	Signal transduction, apoptosis
4-D3ZQ18	NCCRP1, F-box-associated domain-containing	<b>Nccrp1</b>	↑2.9	0.0011	Cytoplasm	Protein ubiquitination
5-D3ZX38	Prefoldin 1	<b>Pfdn1</b>	↑2.6	0.0182	Cytoplasm	Protein folding, actin cytoskeleton organization
6-D3ZKT0	Phosphatidate cytidyltransferase, mitochondrial	<b>Tamm41</b>	↑2.2	0.0188	Cell membrane, mitochondrion	Lipid metabolism
7-A0A0G2JY26	DnaJ heat shock protein family (Hsp40) member C6	<b>Dnajc6</b>	↑2.2	0.0230	Cytoplasm, synapse	Clathrin-mediated endocytosis
8-Q9JKS6	Protein piccolo	<b>Pclo</b>	↑2.1	0.0120	Cell junction, synapse	Regulation of exocytosis
9-Q99J82	Integrin-linked protein kinase	<b>Ilk</b>	↑2.0	0.0054	Cell membrane, cytoplasm	Signal transduction, aging
10-Q510K8	28S ribosomal protein S7, mitochondrial	<b>Mrps7</b>	↑2.0	0.0024	Mitochondrion	Translation
11-O88778	Protein bassoon	<b>Bsn</b>	↑2.0	0.0023	Cell junction, cytoplasm, synapse	Retrograde axonal transport

### Down-regulated

1-Q00438	Polypyrimidine tract-binding protein 1	<b>Ptbp1</b>	↓14.4	0.0031	Nucleus	RNA processing, neurogenesis
2-P50116	Protein S100-A9	<b>S100a9</b>	↓5.4	0.0138	Cell membrane, cytoplasm, secreted	Actin cytoskeleton organization, apoptosis, immunity
3-B2RZ74	U1 small nuclear ribonucleoprotein 70 kDa	<b>Snrnp70</b>	↓4.4	0.0106	Cytoplasm, nucleus	RNA processing
4-F1LRI5	GCN1 activator of EIF2AK4	<b>Gcn111</b>	↓4.3	0.0102	Cytoplasm	Regulation of translation
5-P23562	Band 3 anion transport protein	<b>Slc4a1</b>	↓3.5	0.0390	Cell membrane	Ion transport

6-Q63798	Proteasome activator complex subunit 2	<b>Psme2</b>	↓3.2	0.0309	Cytoplasm, nucleus	Antigen processing, cell cycle
7-F1LRS8	CD2-associated protein	<b>Cd2ap</b>	↓3.2	0.0172	Cytoplasm, cytoskeleton	Actin cytoskeleton organization, cell cycle
8-Q63797	Proteasome activator complex subunit 1	<b>Psme1</b>	↓3.0	0.0102	Cytoplasm, nucleus	Antigen processing, cell cycle
9-Q5U2Y1	General transcription factor II-I	<b>Gtf2i</b>	↓2.9	0.0409	Cytoplasm, nucleus	Regulation of transcription
10-A0A0G2JSV6	Globin c2	<b>Hba-a2</b>	↓2.6	0.0045	Cytoplasm, secreted	Oxygen transport
11-Q62667	Major vault protein	<b>Mvp</b>	↓2.4	0.0047	Cytoplasm, nucleus	Signal transduction
12-Q4KLZ3	DAZ-associated protein 1	<b>Dazap1</b>	↓2.4	0.0267	Cytoplasm, nucleus	RNA processing
13-P17475	Alpha-1-antitrypsin	<b>Serpina1</b>	↓2.3	0.0009	Secreted	Inflammatory response
14-Q5XIE0	Acidic leucine-rich nuclear phosphoprotein 32 family member E	<b>Anp32e</b>	↓2.3	0.0461	Cytoplasm, nucleus	Protein folding, apoptosis
15-P0C643	RAS guanyl-releasing protein 2	<b>Rasgrp2</b>	↓2.3	0.0198	Cell membrane, cytoplasm, synapse	Signal transduction
16-P25886	60S ribosomal protein L29	<b>Rpl29</b>	↓2.3	0.0013	Ribosome, synapse	Aging, translation
17-Q63041	Alpha-1-macroglobulin	<b>A1m</b>	↓2.0	0.0003	Secreted	Protease inhibitor
18-Q6IMY8	Heterogeneous nuclear ribonucleoprotein U	<b>Hnrnpu</b>	↓2.0	0.0031	Nucleus, cytoplasm	RNA processing, cell cycle
19-Q3B8Q1	Nucleolar RNA helicase 2	<b>Ddx21</b>	↓2.0	0.0093	Cytoplasm, nucleus, mitochondrion	Immunity, RNA processing
20-D3ZQG6	Tripartite motif-containing protein 2	<b>Trim2</b>	↓2.0	0.0012	Cytoplasm	Protein ubiquitination, apoptosis

c) Subcellular localization and function of altered proteins isolated from **rat hippocampus** after 7-day treatment with **morphine, LYS739** and **LYS744** (**3 mg/kg**) identified by label-free quantification (MaxLFQ).

Accession number	Protein name	Gene	Change (fold)	p value	Subcellular localization	Molecular functions and biological processes- keywords
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### HIPPOCAMPUS -MORPHINE – 3 mg/kg, 7 days

#### UP-regulated

1-A0A0G2K9C0	Vasodilator-stimulated phosphoprotein	<b>Vasp</b>	↑4.1	0.0497	Cytoplasm, cytoskeleton	Actin cytoskeleton organization
2-M0R7B4	H1.3 linker histone, cluster member	<b>Hist1h1d</b>	↑2.8	<0.0001	Nucleus	DNA processing, nucleus assembly
3-P31232	Transgelin	<b>Tagln</b>	↑2.7	<0.0001	Cytoplasm	Actin filament binding
4-Q00566	Methyl-CpG-binding protein 2	<b>Mecp2</b>	↑2.6	0.009	Nucleus	RNA processing
5-Q5U2Y1	General transcription factor II-I	<b>Gtf2i</b>	↑2.2	0.0213	Cytoplasm, nucleus	Regulation of transcription
6-A1A5S2	CXXC-type zinc finger protein 1	<b>Cxxc1</b>	↑2.2	0.0210	Nucleus	Regulation of transcription
7-P27791	cAMP-dependent protein kinase catalytic subunit alpha	<b>Prkaca</b>	↑2.0	0.0441	Cell membrane, cytoplasm, mitochondrion	Signal transduction

8-P25886	60S ribosomal protein L29	<b>Rpl29</b>	↑2.0	0.0051	Ribosome, synapse	Aging, translation
<b>Down-regulated</b>						
1-Q6AXS3	Protein DEK	<b>Dek</b>	↓2.7	0.0121	Nucleus	Chromatin organization
2-A0A0G2JSV6	Globin c2	<b>Hba-a2</b>	↓2.7	0.0158	Cytoplasm, secreted	Oxygen transport
3-F1LMV6	Desmoplakin	<b>Dsp</b>	↓2.5	0.0001	Cytoplasm, cytoskeleton	Desmosome organization, cell-cell adhesion
4-Q64542	Plasma membrane calcium-transporting ATPase 4	<b>Atp2b4</b>	↓2.5	0.0109	Cell membrane	Calcium transport, hippocampus development
5-P23565	Alpha-internexin	<b>Ina</b>	↓2.2	0.0015	Cytoplasm, cytoskeleton	Cytoskeleton organization, developmental protein
6-Q6P0K8	Junction plakoglobin	<b>Jup</b>	↓2.2	0.0003	Cytoplasm, cytoskeleton, cell junction	Cell-cell adhesion, desmosome assembly

## HIPPOCAMPUS -LYS739 – 3 mg/kg, 7 days

### UP-regulated

1-M0R7B4	H1.3 linker histone, cluster member	<b>Hist1h1d</b>	↑4.5	<0.0001	Nucleus	DNA processing, nucleus assembly
2-Q00566	Methyl-CpG-binding protein 2	<b>Mecp2</b>	↑3.9	0.0056	Nucleus	RNA processing
3-Q6MG61	Chloride intracellular channel protein 1	<b>Clic1</b>	↑3.5	0.0095	Cell membrane, cytoplasm, nucleus	Ion transport
4-Q5XIP6	Flap endonuclease 1	<b>Fen1</b>	↑3.0	0.0339	Mitochondrion, nucleus	DNA processing
5-Q03344	ATPase inhibitor, mitochondrial	<b>Atpif1</b>	↑2.5	0.0031	Mitochondrion	Regulation of ATP metabolic process
6-D3ZQG6	Tripartite motif-containing protein 2	<b>Trim2</b>	↑2.2	<0.0001	Cytoplasm	Protein ubiquitination, apoptosis
7-Q62703	Reticulocalbin-2	<b>Rcn2</b>	↑2.1	0.0113	Endoplasmic reticulum	Calcium ion binding
8-P07150	Annexin A1	<b>Anxa1</b>	↑2.0	0.0022	Cell membrane, cytoplasm, endosome, nucleus	Immunity, signal transduction

### Down-regulated

1-D4A510	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily c, member 2	<b>Smarcc2</b>	↓4.8	0.0364	Nucleus	Regulation of transcription
2-C0JPT7	Filamin A	<b>Flna</b>	↓4.2	0.0238	Cell membrane, cytoplasm, nucleus, GA	Actin cytoskeleton organization
3-Q5FVI4	Cell cycle exit and neuronal differentiation protein 1	<b>Cend1</b>	↓3.9	<0.0001	Cell membrane	Neuronal differentiation
4-Q62733	Lamina-associated polypeptide 2, isoform beta	<b>Tmpo</b>	↓3.7	0.0280	Nucleus	Regulation of transcription
5-P16884	Neurofilament heavy polypeptide	<b>Nefh</b>	↓3.7	0.0016	Cytoplasm, cytoskeleton	Brain development, cytoskeleton organization
6-P37361	Metallothionein-3	<b>Mt3</b>	↓3.5	0.0040	Cytoplasm, mitochondrion, nucleus, ER	Ion homeostasis, brain development, oxidative stress
7-P24594	Insulin-like growth factor-binding protein 5	<b>Igfbp5</b>	↓3.0	0.0025	Secreted	Aging, signal transduction

8-B2RYJ4	L-aminoadipate-semialdehyde dehydrogenase-phosphopantetheinyl transferase	<b>Aasdhppt</b>	↓3.0	0.0232	Cytoplasm	Vitamin B5 metabolism
9-D3ZRG7	RNA-binding motif protein 26	<b>Rbm26</b>	↓2.9	<0.0001	Nucleus	RNA processing
10-D3ZUV3	Eukaryotic translation initiation factor 2A	<b>Eif2a</b>	↓2.8	0.0126	Cytoplasm	Regulation of translation
11-P06302	Prothymosin alpha	<b>Ptma</b>	↓2.7	0.0099	Nucleus	Cell differentiation, apoptosis
12-Q62876	Synaptogyrin-1	<b>Syng1</b>	↓2.7	0.0013	Melanosome	Exocytosis
13-P49806	Regulator of G-protein signaling 10	<b>Rgs10</b>	↓2.6	0.0032	Cytoplasm, nucleus	Signal transduction
14-Q91XQ4	DNA-directed RNA polymerase II subunit GRINL1A	<b>Polr2m</b>	↓2.6	0.0087	Nucleus	Regulation of transcription, signal transduction
15-D4AAZ6	60S ribosomal protein L37a	<b>Rpl37a</b>	↓2.5	0.0100	Cytoplasm	Regulation of translation
16-Q2LAP6	Testin	<b>Tes</b>	↓2.4	0.0114	Cytoplasm	Cell proliferation, cell adhesion
17-P02625	Parvalbumin alpha	<b>Pvalb</b>	↓2.4	0.0014	Cytoplasm, nucleus	Calcium-binding protein
18-P05505	Cytochrome c oxidase subunit 3	<b>Mtco3</b>	↓2.3	0.0331	Mitochondrion	Respiratory electron transport
19-P63055	Purkinje cell protein 4	<b>Pcp4</b>	↓2.3	0.0188	Cytoplasm, cytoskeleton	Signal transduction, apoptosis
20-Q63186	Translation initiation factor eIF-2B subunit delta	<b>Eif2b4</b>	↓2.2	0.0274	Cytoplasm	Regulation of translation, brain development
21-Q925G1	Hepatoma-derived growth factor-related protein 2	<b>Hdgfrp2</b>	↓2.2	0.0192	Nucleus	Regulation of cell growth, RNA processing
22-B5DES0	Small nuclear ribonucleoprotein Sm D2	<b>Snrpd2</b>	↓2.1	0.0217	Cytoplasm, nucleus	RNA processing
23-Q63910	Alpha globin	<b>Hba-a3</b>	↓2.1	0.0007	Cytoplasm, secreted	Oxygen transport
24-D3ZXH7	Aly/REF export factor	<b>Alyref</b>	↓2.1	0.0192	Cytoplasm, nucleus	RNA processing
25-P23565	Alpha-internexin	<b>Ina</b>	↓2.0	<0.0001	Cytoplasm, cytoskeleton	Cytoskeleton organization, developmental protein
26-Q64542	Plasma membrane calcium-transporting ATPase 4	<b>Atp2b4</b>	↓2.0	0.0289	Cell membrane	Calcium transport, hippocampus development
27-P30009	Myristoylated alanine-rich C-kinase substrate	<b>Marcks</b>	↓2.0	0.0029	Cytoplasm, cytoskeleton, cell membrane	Actin filament organization, brain development
28-D4A9L2	Serine/arginine-rich splicing factor 1	<b>Srsf1</b>	↓2.0	0.0201	Cytoplasm, nucleus	RNA processing

## HIPPOCAMPUS-LYS744 – 3 mg/kg, 7 days

### UP-regulated

1-E9PTB2	Transcription elongation factor SPT5	<b>Supt5h</b>	↑4.5	0.0036	Nucleus	Regulation of transcription
2-Q71UF4	Histone-binding protein RBBP7	<b>Rbbp7</b>	↑4.4	0.0404	Nucleus	Regulation of transcription
3-A0A096MIX2	RNA helicase	<b>Ddx17</b>	↑3.9	0.0067	Cytoplasm, nucleus	RNA processing
4-Q6MG61	Chloride intracellular channel protein 1	<b>Clic1</b>	↑3.2	0.0372	Cell membrane, cytoplasm, nucleus	Ion transport
5-Q9JM53	Apoptosis-inducing factor 1, mitochondrial	<b>Aifm1</b>	↑3.1	0.0187	Cytoplasm, mitochondrion, nucleus	Apoptosis
6-M0R7B4	H1.3 linker histone, cluster member	<b>Hist1h1d</b>	↑2.7	0.0002	Nucleus	DNA processing, nucleus assembly
7-Q00566	Methyl-CpG-binding protein 2	<b>Mecp2</b>	↑2.6	0.0134	Nucleus	RNA processing

<b>8-Q6UPE1</b>	Electron transfer flavoprotein-ubiquinone oxidoreductase, mitochondrial	<b>Etfdh</b>	↑2.6	0.0016	Mitochondrion	Electron transport chain
<b>9-Q03344</b>	ATPase inhibitor, mitochondrial	<b>Atpif1</b>	↑2.4	0.0037	Mitochondrion	Regulation of ATP metabolic process
<b>10-Q62745</b>	CD81 antigen	<b>Cd81</b>	↑2.4	0.0274	Cell membrane	Immunity
<b>11-D3ZZ21</b>	Complex I-B17	<b>Ndufb6</b>	↑2.4	0.0003	Mitochondrion	Respiratory electron transport
<b>12-P00406</b>	Cytochrome c oxidase subunit 2	<b>Mtco2</b>	↑2.3	0.0008	Mitochondrion	Respiratory electron transport
<b>13-P35559</b>	Insulin-degrading enzyme	<b>Ide</b>	↑2.2	0.0040	Cell membrane, cytoplasm, secreted	Insulin metabolism, proteolysis
<b>14-Q00959</b>	Glutamate receptor ionotropic, NMDA 2A	<b>Grin2a</b>	↑2.1	0.0156	Cell membrane, synapse	Ion transport, brain development
<b>15-Q63881</b>	Potassium voltage-gated channel subfamily D member 2	<b>Kcnd2</b>	↑2.1	0.0054	Cell membrane, synapse	Ion transport
<b>16-D4ADE5</b>	Histone-lysine N-methyltransferase SETD7	<b>Setd7</b>	↑2.1	0.0092	Nucleus	Regulation of transcription
<b>17-P21396</b>	Amine oxidase [flavin-containing] A	<b>Maoa</b>	↑2.0	0.0109	Mitochondrion	Catecholamine metabolism
<b>18-P01015</b>	Angiotensinogen	<b>Agt</b>	↑2.0	0.0462	Secreted	Vasoconstrictor, aging
<b>19-Q63345</b>	Myelin-oligodendrocyte glycoprotein	<b>Mog</b>	↑2.0	<0.0001	Cell membrane	Cell adhesion, aging
<b>20-P07722</b>	Myelin-associated glycoprotein	<b>Mag</b>	↑2.0	0.0005	Cell membrane	Cell adhesion, axon regeneration
<b>21-Q4V7A0</b>	WD repeat-containing protein 61	<b>Wdr61</b>	↑2.0	0.0219	Cytoplasm, nucleus	Regulation of transcription
<b>22-P25886</b>	60S ribosomal protein L29	<b>Rpl29</b>	↑2.0	0.0083	Ribosome, synapse	Aging, translation
<b>23-Q99P82</b>	Claudin-11	<b>Cldn11</b>	↑2.0	0.0029	Cell membrane	Cell adhesion
<b>24-Q07647</b>	Solute carrier family 2, facilitated glucose transporter member 3	<b>Slc2a3</b>	↑2.0	0.0268	Cell membrane	Glucose transport

### ***Down-regulated***

<b>1-C0JPT7</b>	Filamin A	<b>Flna</b>	↓5.5	0.0115	Cell membrane, cytoplasm, nucleus, GA	Actin cytoskeleton organization
<b>2-P16884</b>	Neurofilament heavy polypeptide	<b>Nefh</b>	↓4.2	0.0004	Cytoplasm, cytoskeleton	Brain development, cytoskeleton organization
<b>3-Q91XQ4</b>	DNA-directed RNA polymerase II subunit GRINL1A	<b>Polr2m</b>	↓3.3	0.0048	Nucleus	Regulation of transcription, signal transduction
<b>4-Q6AYJ8</b>	Tumor necrosis factor alpha-induced protein 8-like protein 2	<b>Tnfaip8l2</b>	↓2.9	0.0488	Cytoplasm	Immunity, apoptosis
<b>5-P02625</b>	Parvalbumin alpha	<b>Pvalb</b>	↓2.7	0.0007	Cytoplasm, nucleus	Calcium-binding protein
<b>6-P24594</b>	Insulin-like growth factor-binding protein 5	<b>Igfbp5</b>	↓2.7	0.0305	Secreted	Aging, signal transduction
<b>7-P63055</b>	Purkinje cell protein 4	<b>Pcp4</b>	↓2.5	<0.0001	Cytoplasm, cytoskeleton	Signal transduction, apoptosis
<b>8-D3ZRG7</b>	RNA-binding motif protein 26	<b>Rbm26</b>	↓2.4	0.0089	Nucleus	RNA processing
<b>9-F1LMV6</b>	Desmoplakin	<b>Dsp</b>	↓2.4	<0.0001	Cytoplasm, cytoskeleton	Desmosome organization, cell-cell adhesion
<b>10-B5DES0</b>	Small nuclear ribonucleoprotein Sm D2	<b>Snrpd2</b>	↓2.3	0.0023	Cytoplasm, nucleus	RNA processing
<b>11-Q5FVI4</b>	Cell cycle exit and neuronal differentiation protein 1	<b>Cend1</b>	↓2.2	0.0036	Cell membrane	Neuronal differentiation
<b>12-Q62876</b>	Synaptogyrin-1	<b>Syng1</b>	↓2.2	0.0054	Melanosome	Exocytosis
<b>13-Q6P0K8</b>	Junction plakoglobin	<b>Jup</b>	↓2.1	<0.0001	Cytoplasm, cytoskeleton, cell junction	Cell-cell adhesion, desmosome assembly

<b>14-Q63910</b>	Alpha globin	<b>Hba-a3</b>	↓2.1	0.0079	Cytoplasm, secreted	Oxygen transport
<b>15-P06302</b>	Prothymosin alpha	<b>Ptma</b>	↓2.1	0.0483	Nucleus	Cell differentiation, apoptosis
<b>16-P21818</b>	Stathmin-2	<b>Stmn2</b>	↓2.0	0.0053	Cytoplasm, endosome, GA	Regulator of microtubule stability
<b>17-Q9EPJ0</b>	Nuclear ubiquitous casein and cyclin-dependent kinase substrate 1	<b>Nucks1</b>	↓2.0	<0.0001	Nucleus	DNA processing
<b>18-Q5M9G1</b>	Protein HEXIM1	<b>Hexim1</b>	↓2.0	0.0009	Cytoplasm, nucleus	Immunity, regulation of transcription

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\*GA – Golgi apparatus

\*\*ER – Endoplasmic reticulum