

Table S-1 The sequences of primers

Primer name	Primer sequence
DDC	5'-TTCTTCGTGGTTGTCACCTAG-3'
	5'-AGATACCGAACTCAGGACAGA-3'
Comt	5'-GCCTACAGGACAAAGTCACCA-3'
	5'-AAGTGTGTCTGGAAGGTAGCG-3'
MAO	5'-AACCCGAGTCCAAGGATGTTTC-3'
	5'-GCAGAGAAGAGCCACAGAAGT-3'
Gad67	5'-GCTTGGCTTTGGAAGTACCAATGTG-3'
	5'-CAGTCGTGCCTGCGGTTGC-3'
Dbh	5'-ACCTCTGCCGTCCTCC-3'
	5'-CTGCCTCCGTGGTGATGACAAC-3'
TH	5'-AGCGCCATTCTCTGTGAAG-3'
	5'-CTGTGGGTGGTACCCTATGC-3'
ACHE	5'-GCTCGGGTCTATGCCTACATCTTTG-3'
	5'-TTCTCTCCTCCACGGTGTAGTTCAG-3'

Table S-2 Summary of the linear range and regression equation, LOD and LOQ results of the LC-QE-MS method for the analyzed quality control samples

Neurotransmitters	Linear range ng·mL <sup>-1</sup>	Regression equation	r	LOD ng·mL <sup>-1</sup>	LOQ ng·mL <sup>-1</sup>
L-Histidine	2.5-1000	Y = -0.000123575+0.000651925*X	0.9992	0.10	0.30
Histamine	2.5-1000	Y = -0.0027685+0.00105485*X	0.9997	0.20	0.50
L-Ornithine	2.5-1000	Y = -0.000320582+0.000178781*X	0.9980	0.30	1.00
L-Tyrosine	100-5000	Y=0.00612046+0.000645315*X	0.9975	0.30	1.00
Homovanillic acid	100-5000	Y = 0.00199248+7.16219e-005*X	0.9945	1.00	5.00
L-Citrulline	2.5-1000	Y = 0.00395988+0.000867413*X	0.9947	1.50	5.00
L-Glutamine	100-5000	Y = 0.0534283+0.00109105*X	0.9900	1.50	5.00
L-Glutamate	50-20000	Y = 0.0718867+0.000518421*X	0.9979	0.20	1.00
Γ-Aminobutyric acid	50-20000	Y= 0.0348965+0.000505073*X	0.9996	0.10	1.00
L-Proline	2.5-1000	Y = 0.00503059+0.00175473*X	0.9978	0.30	1.00
Epinephrine	100-5000	Y = 0.110632+0.00128883*X	0.9984	0.20	0.50
Choline	100-5000	Y = 0.149382+0.00081938*X	0.9951	0.20	0.50
Dopamine	100-5000	Y = 0.00750808+6.2054e-005*X	0.9952	0.30	2.00
L-Phenylalanine	100-5000	Y = 0.105773+0.00134366*X	0.9928	0.30	0.50
Acetylcholine	2.5-1000	Y = 0.00890604+0.00483898*X	0.9995	0.30	2.00
5-hydroxyindoleacetic acid	2.5-1000	Y = -0.000589054+0.000207323*X	0.9925	1.00	10.00
L-Arginine	2.5-1000	Y = 0.00070588+0.000656132*X	0.9911	0.20	0.50
Levodopa	2.5-1000	Y = 0.000462291+0.000271332*X	0.9987	0.20	2.00
L-Threonine	2.5-1000	Y = 0.00989336+0.0561152*X	0.9943	0.30	1.00

Hydroxyproline	2.5-1000	$Y = 0.00934336 + 0.00114152 * X$	0.9957	0.30	1.00
L-Methionine	2.5-1000	$Y = 0.000868367 + 0.000604462 * X$	0.9977	0.60	2.00
L-Serine	2.5-1000	$Y = 0.00239734 + 0.000476314 * X$	0.9986	0.20	0.50
L-Leucine	100-5000	$Y = 0.338652 + 0.00317502 * X$	0.9902	0.30	1.00

Table S-3 Summary of the accuracy and precision results of the LC-QE-MS method for the analyzed quality control samples

Neurotransmitters	Intraday precision		Inter-day precision	
	accuracy	precision	accuracy	precision
	(%)	(RSD,%)	(%)	(RSD,%)
L-Histidine	85.74-112.7	3.55-12.75	78.27-99.59	11.07-15.77
Histamine	82.61-106.83	0.8-13.04	80.21-99.93	0.76-14.66
L-Ornithine	77.11-87.92	1.16-9.60	73.54-87.92	1.54-12.29
L-Tyrosine	85.46-102.6	0.25-3.28	82.69-100.2	2.16-4.39
Homovanillic acid	83.74-94.94	0.63-6.72	78.9-92.55	0.6-12.69
L-Citrulline	74.64-100.39	1.66-12.57	77.67-107.64	3.13-14.08
L-Glutamine	81.17-105.74	3.35-11.04	75.39-98.82	8.65-12.01
L-Glutamate	89.48-95.82	1.51-6.80	86.03-90.87	3.48-7.61
Γ-Aminobutyric acid	93.04-98.82	1.29-1.42	88.72-98.33	2.48-8.86
L-Proline	74.45-89.91	1.35-4.19	71.05-87.77	2.81-14.70
Epinephrine	83.17-91.41	0.89-7.19	78.22-81.14	8.03-14.92
Choline	83.45-128.25	1.22-6.11	76.12-116.94	3.5-13.84
Dopamine	84.69-103.1	1.82-11.13	81.68-103.1	1.73-11.08
L-Phenylalanine	86.04-89.48	2.9-11.42	81.84-86.04	4.6-13.11
Acetylcholine	81.60-91.34	1.87-4.89	77.83-81.03	6.91-17.84
5-hydroxyindoleacetic acid	80.55-102.51	2.81-6.76	70.12-95.54	4.27-17.4
L-Arginine	89.02-112.61	2.32-10.65	81.77-96.85	14.68-18.4
Levodopa	83.36-88.23	1.52-8.9	80.88-82.16	2.42-11.91
L-Threonine	77.98-112.82	1.82-9.14	71.11-109.89	3.55-16.04
Hydroxyproline	80.95-113.84	1.17-10.51	80.28-110.99	2.97-8.36
L-Methionine	75.15-83.00	2.74-21.91	70.14-80.03	4.49-23.83
L-Serine	85.03-126.13	0.24-6.03	79.54-122.09	3.80-13.15
L-Leucine	83.04-125.67	0.48-11.72	83.04-122.39	2.88-11.18

Table S-4 Summary of the accuracy and stability results of the LC-QE-MS method for the analyzed quality control samples.

Neurotransmitters	intraday stability		inter-day stability	
	accuracy	stability	accuracy	stability
	(%)	(RSD,%)	(%)	(RSD,%)
L-Histidine	83.72-106.08	2.4-9.93	75.57-91.95	11.99-19.93
Histamine	83.17-97.81	0.51-3.01	80.51-99.78	1.56-8.58
L-Ornithine	77.18-92.63	1.79-4.70	73.27-85.89	6.5-8.93
L-Tyrosine	86.86-103.01	1.12-2.27	83.86-100.55	2.46-4.13
Homovanillic acid	82.81-95.68	0.57-5.05	83.44-93.03	3.36-12.37
L-Citrulline	74.67-111.27	1.63-18.51	71.07-108.45	2.94-19.78

L-Glutamine	79.52-102.91	3.32-4.78	74.04-97.30	7.07-9.77
L-Glutamate	89.12-92.32	1.39-3.58	85.94-87.61	4.27-6.26
Γ-Aminobutyric acid	93.51-97.77	0.93-3.33	89.26-97.80	2.44-5.32
L-Proline	71.81-96.14	1.61-12.59	70.58-90.25	3.47-19.24
Epinephrine	83.6-88.05	1.18-4.19	77.58-84.70	4.82-14.96
Choline	79.83-122.69	1.01-4.66	73.52-111.55	4.00-12.5
Dopamine	87.72-102.94	0.8-2.33	80.76-100.03	313-13.02
L-Phenylalanine	87.31-93.22	1.76-4.41	81.78-84.23	4.15-12.14
Acetylcholine	80.72-94.52	0.94-10.10	75.93-84.59	4.41-20.45
5-hydroxyindoleacetic acid	85.93-101.47	1.80-7.14	75.25-94.87	3.70-16.91
L-Arginine	88.49-114.01	1.15-7.81	78.25-100.15	15.12-20.26
Levodopa	82.37-87.91	0.85-8.37	80.36-81.67	2.75-14.68
L-Threonine	76.87-113.44	0.75-20.27	71.11-110.58	2.82-26.38
Hydroxyproline	85.93-112.93	0.69-14.29	80.58-110.03	3.05-17.17
L-Methionine	71.28-81.50	1.16-21.9	70.1-78.61	3.98-18.3
L-Serine	85.11-128.63	1.06-14.01	79.55-126.31	2.13-19.24
L-Leucine	82.25-126.67	0.73-5.64	80.14-123.90	2.72-11.58

Table S-5 MS parameters of 23 measured neurotransmitters

NO	Name	Precursor ion (m/z)	Product ion (m/z)
1	L-Histidine	156.07655	110.07159,95.06085,83.06102
2	Histamine	112.01810	88.08488,57.04567
3	L-Ornithine	133.09712	90.05555,87.05599
4	L-Tyrosine	182.08087	165.05457,137.07565,147.04398,136.07565,123.04420
5	Homovanillic acid	165.05444	137.05969,123.04418,147.04420,119.04940
6	L-Citrulline	176.10266	130.03226,84.04508
7	L-Glutamine	147.07613	130.04997,119.04942,102.05540
8	L-Glutamate	148.06013	130.04997,102.05540,84.04503
9	Γ-Aminobutyric acid	104.10741	87.04469,60.08165,69.03430,86.06069
10	L-Proline	116.07075	70.06584
11	Epinephrine	166.08597	149.02673,74.02440
12	Choline	104.10714	87.04469,69.04430,60.08165
13	Dopamine	136.07547	126.95537,119.03554
14	L-Phenylalanine	166.08626	120.08101,103.05469
15	Acetylcholine	146.11737	87.04470,84.04506,130.05000
16	5-hydroxyindoleacetic acid	192.06516	146.06006,107.96027
17	L-Arginine	175.11870	116.07085,130.07953,70.06589
18	Levodopa	198.07603	152.07086,135.04402
19	L-Threonine	120.06567	102.05542,74.06078,56.05039
20	Hydroxyproline	132.10173	86.09708

21	L-Methionine	150.05803	133.03185,104.05327,56.05039
22	L-Serine	106.05018	79.05502,60.04528
23	L-Leucine	132..07657	112.84048,13.07657,87.10034,86.09708
24	IS	290.10944	262.11490,.227.14618,119.11969,154.04160

Table S-6. The content for neurotransmitters of restored by OA in brain samples. (\*P < 0.05,\*\*P < 0.01 compared to the SHR group.(ug/g, n = 6)

	Hippocampus			Striatum		
	Control group	SHR group	OA group	Control group	SHR group	OA group
L-Histidine	0.00104±0.00006	0.00129±0.00039	0.00117±0.00022	3.032±1.039*	4.197±0.739	3.082±0.837*
Histamine	0.073±0.002	0.075±0.001	0.073±0.001	0.074±0.002	0.076±0.002	0.076±0.002
L-Ornithine	0.519±0.091**	0.349±0.038	0.569±0.203**	0.603±0.117	0.923±0.386	0.604±0.182
L-Tyrosine	32.257±1.9	34.162±5.737	41.163±3.773*	73.228±17.142**	34.436±1.686	53.761±9.358**
Homovanillic acid	40.034±3.388**	56.702±3.709	53.134±5.222	29.524±1.35**	61.563±15.589	37.188±2.813**
L-Citrulline	0.342±0.021*	0.215±0.06	0.315±0.072*	0.144±0.059**	0.577±0.285	0.295±0.073*
L-Glutamine	29.584±5.12**	59.214±5.199	39.622±9.634**	42.193±4.391**	97.92±22.589	47.202±6.208**
L-Glutamate	103.251±19.596**	224.503±16.906	163.426±27.188*	148.568±27.805**	325.401±115.914	155.541±25.056**
Γ-Aminobutyric acid	174.697±25.467*	123.964±30.612	180.278±37.429**	225.675±61.667**	148.568±27.805	193.644±21.566**
L-Proline	6.334±0.473*	5.364±0.603	9.129±2.047**	5.937±0.77**	9.703±2.854	6.998±1.183*
Epinephrine	45.219±5.711	47.302±2.949	42.914±4.781	43.097±8.11**	65.247±12.203	45.942±4.641**
Choline	98.73±7.489**	132.65±14.465	126.135±14.729	128.202±25.356**	196.835±22.373	141.335±27.999**
Dopamine	38.873±3.069**	56.777±4.1	54.197±6.997	29.746±1.338**	53.946±12.612	37.339±2.673**
L-Phenylalanine	59.449±9.715**	39.309±4.406	55.27±7.867**	40.506±6.485	52.431±16.705	44.624±4.178

Acetylcholine	0.324±0.108**	1.081±0.155	0.556±0.108**	0.586±0.181**	1.289±0.217	0.653±0.133**
5-hydroxyindoleacetic acid	0.906±0.081**	1.338±0.07	1.056±0.12**	0.581±0.175	0.781±0.153	0.738±0.071
L-Arginine	12.542±1.418**	6.537±0.6	11.306±1.758**	9.441±2.256	14.736±5.969	9.869±2.562*
Levodopa	—	—	—	0.358±0.067**	0.731±0.691	0.316±0.114**

	Hypothalamus			Temporal lobe		
	Control group	SHR group	OA group	Control group	SHR group	OA group
L-Histidine	1.95±0.214*	2.795±0.833	2.09±0.211*	1.705±0.438*	3.129±0.961	2.234±0.228
Histamine	0.126±0.013*	0.338±0.132	0.209±0.044*	0.073±0.001	0.074±0.004	0.073±0.001
L-Ornithine	1.011±0.149*	0.795±0.123	1.014±0.198*	0.506±0.128*	0.376±0.055	0.49±0.254
L-Tyrosine	67.524±14.765**	49.946±4.227	79.237±7.11*	36.923±2.591**	31.28±3.084	44.392±8.563*
Homovanillic acid	68.166±15.316*	111.557±7.791	67.025±6.101*	37.966±4.406	53.046±17.5	36.673±7.774
L-Citrulline	0.387±0.069**	0.24±0.088	0.334±0.082*	0.407±0.053**	0.265±0.065	0.407±0.259
L-Glutamine	68.454±5.016*	70.285±16.764	59.827±5.656	46.07±9.505**	80.111±31.23	51.328±5.454*
L-Glutamate	95.931±17.677**	135.869±20.179	102.396±4.792**	193.027±58.285*	299.114±98.617	192.198±47.583*
Γ-Aminobutyric acid	461.692±78.717*	380.173±54.269	396.224±50.958	229.012±50.247*	161.169±24.791	290.338±218.045*
L-Proline	26.311±26.328**	12.436±1.213	17.199±2.038**	10.331±3.374*	7.64±1.157	8.035±2.429

Epinephrine	72.548±14.035**	112.498±28.239	68.486±10.964**	26.814±2.377**	53.695±37.317	26.269±3.935*
Choline	227.179±19.731*	249.843±40.423	240.322±22.486	98.979±14.946*	130.152±48.219	98.168±21.321*
Dopamine	67.261±6.512**	95.323±25.379	71.469±5.8*	42.173±4.999	38.283±4.772	49.224±7.728
L-Phenylalanine	96.589±20.782*	59.848±10.641	70.596±15.071	47.578±2.924*	34.356±7.182	43.479±5.118
Acetylcholine	0.298±0.127*	0.576±0.19	0.359±0.034*	0.449±0.096**	0.987±0.281	0.531±0.103**
5-hydroxyindoleacetic acid	1.466±0.546*	2.255±0.755	2.102±0.22	0.926±0.124	0.889±0.095	1.322±0.186**
L-Arginine	14.351±3.175*	11.033±1.93	15.48±1.949**	9.344±3.827*	5.979±1.489	9.224±9.063
Levodopa	—	—	—	—	—	—

Frontal lobe

	Control group	SHR group	OA group
L-Histidine	2.063±0.406	2.586±0.422	2.342±0.633
Histamine	0.0708±0.0004	0.0717±0.001	0.0706±0.0003
L-Ornithine	0.622±0.069*	0.493±0.099	0.518±0.104
L-Tyrosine	53.375±7.729	49.529±5.389	52.57±10.288
Homovanillic acid	43.923±3.095	50.551±4.322	45.36±8.699
L-Citrulline	0.51±0.056	0.433±0.11	0.58±0.304

L-Glutamine	48.216±6.012**	60.765±4.791	54.08±8.201
L-Glutamate	210.164±12.611	223.073±31.644	204.29±18.386
Γ-Aminobutyric acid	304.143±33.53*	202.991±23.354	248.258±54.725
L-Proline	8.145±0.377	7.626±1.274	7.865±1.035
Epinephrine	59.387±11.214	62.103±5.288	56.295±8.331
Choline	141.079±9.732**	117.217±7.07	126.854±9.958
Dopamine	43.495±3.335*	49.265±4.433	44.318±9.089
L-Phenylalanine	69.77±13.007*	55.332±3.499	66.41±25.956
Acetylcholine	1±0.113	0.845±0.214	0.883±0.158
5-hydroxyindoleacetic acid	1.33±0.09*	0.935±0.345	1.415±0.236**
L-Arginine	8.473±1.585	6.613±0.941	7.951±2.242
Levodopa	—	—	—

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**Figure legends**

Fig. S-1 Representative LC/MS total ion current (TIC) chromatograms. LC/MS TIC chromatograms of five brain regions from SHR group, OA group, and control group A hippocampus, B striatum, C hypothalamus, D temporal lobe, E frontal lobe

Fig.S-2 The network of the neurotransmitters and relative expression levels of metabolic-related enzymes show variation for SHRs with or without OA modulation.

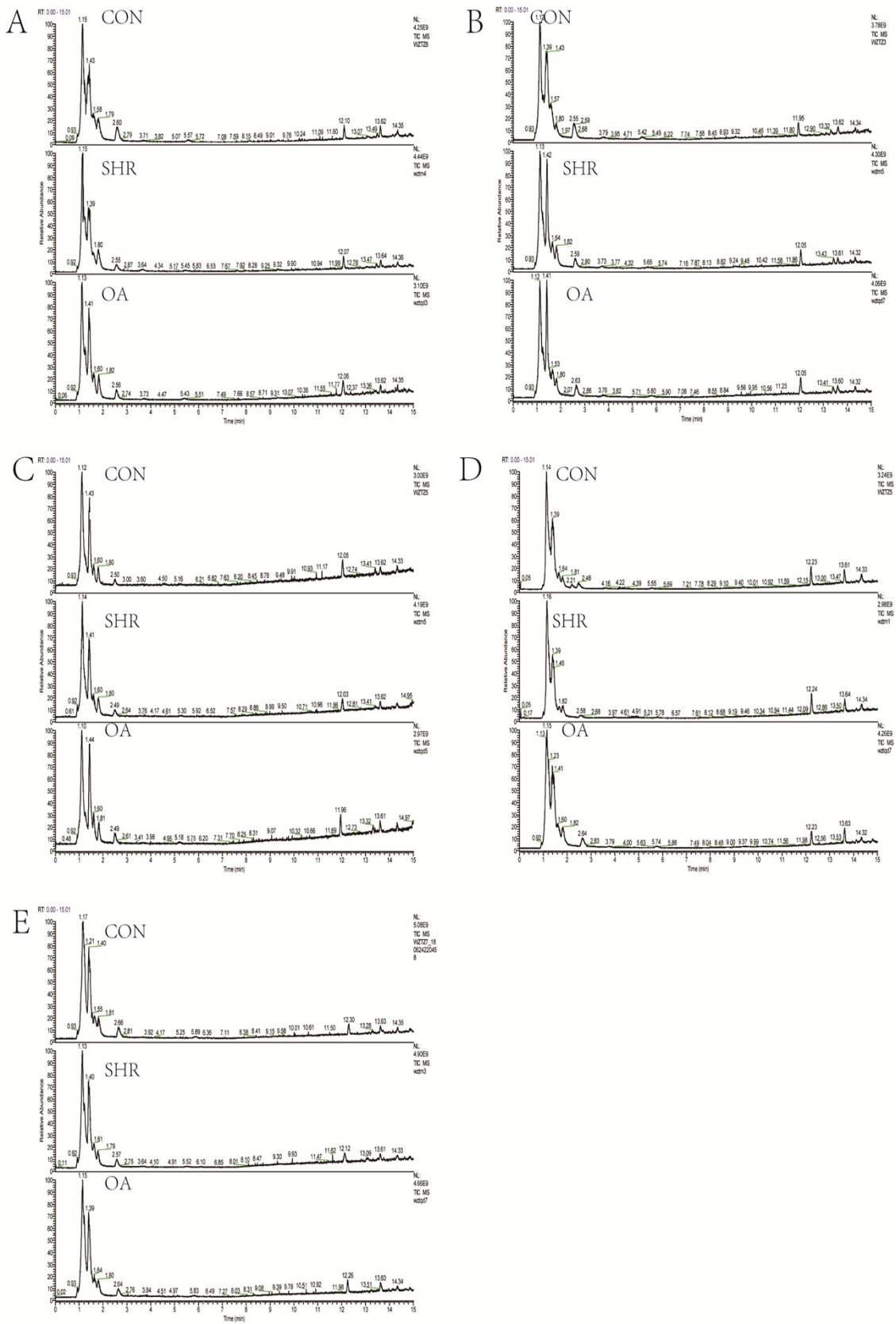


Fig.

