

Table 4 Effects of methamphetamine administration on weight loss in ED-METH group on day 1-14

Group	Weight loss (grams/day)						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Control	6.9 ± 2.01	13.5 ± 2.37	19.7 ± 1.91	26.9 ± 1.72	37.3 ± 2.22	40.3 ± 2.92	48.5 ± 2.92
ED-METH	7.6 ± 1.39	12.3 ± 1.25	13.6 ± 0.73**	21.3 ± 1.19*	28.2 ± 1.58**	35.5 ± 1.86	37.1 ± 1.99**
Group	Weight loss (grams/day)						
	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Control	55.5 ± 2.57	64.7 ± 2.48	68.1 ± 2.46	72.8 ± 6.86	83.3 ± 2.59	87.5 ± 2.58	92.7 ± 2.84
ED-METH	43.0 ± 2.45**	47.0 ± 2.68***	50.9 ± 2.96***	39.7 ± 4.62**	57.9 ± 3.78***	58.7 ± 3.57***	60.5 ± 3.52***

Note: Animals were treated with saline or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14. Data were presented as Mean ± SEM. ED-METH group (n = 8) and control group (n = 13).

* $p < 0.05$ in comparison with control group by t-test

** $p < 0.01$ in comparison with control group by t-test

*** $p < 0.001$ in comparison with control group by t-test

Table 5 Effects of escalating and binge doses-METH administration on weight loss in all experimental groups on day 15

Group	Weight loss on day 15 (grams/day)
Control	101.14 ± 3.27
ED-METH binge	56.87 ± 5.89 ^{***}
ED-METH	65.95 ± 3.94 ^{***}
AB-METH	89.76 ± 3.81

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

^{***}*p* < 0.001 in comparison with control group by ANOVA post hoc Dunnett test

Table 6 Effects of methamphetamine administration on amount of food intake on day 0-15

Group	Amount of food intake of each day (grams/day)							
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Control	27.1 ± 0.690	23.4 ± 0.798	24.7 ± 0.594	29.3 ± 0.945	30.2 ± 0.563	25.9 ± 0.660	23.9 ± 0.83	22.0 ± 0.46
ED-METH	27.0 ± 0.912	22.3 ± 0.765	22.9 ± 0.785	27.4 ± 1.183	26.1 ± 0.712 ^{***}	25.5 ± 0.69	19.8 ± 1.04 ^{**}	20.2 ± 1.11

Group	Amount of food intake of each day (grams/day)							
	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15
Control	22.4 ± 0.58	20.9 ± 0.63	21.0 ± 0.55	20.4 ± 0.65	21.9 ± 1.21	21.7 ± 0.54	21.1 ± 0.53	21.2 ± 0.70
ED-METH	17.6 ± 0.67 ^{***}	17.5 ± 0.64 ^{**}	18.4 ± 0.90 [*]	16.3 ± 0.65 ^{***}	15.7 ± 0.83 ^{**}	17.8 ± 0.92 ^{**}	15.1 ± 0.82 ^{***}	16.4 ± 0.70 ^{***}

Note: Animals were treated with saline or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14. Data were presented as Mean ± SEM. ED-METH group (n = 8) and control group (n = 13).

* $p < 0.05$ in comparison with control group by t-test

** $p < 0.01$ in comparison with control group by t-test

*** $p < 0.001$ in comparison with control group by t-test

Table 7 Effects of METH administration on amount of food intake in each group on day 15 (before binge doses-METH) and day 16 (after binge doses-METH)

	Group	Number of group	Food intake (grams/day)
Day 15	Control	13	21.2 ± 0.70 ^{***}
	ED-effect	8	16.4 ± 0.70 ^{***}
Day 16	Control	12	21.1 ± 0.64 ^{***}
	Binge-effect	9	10.8 ± 1.18 ^{***}

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

^{***} $p < 0.001$ in comparison with control group by t-test

Table 8 Effects of METH administration on core body temperature in all experimental groups on day 15

Group	Core body temperature on day 15 (°C)
Control	36.2 ± 0.19
ED-METH binge	37.0 ± 0.27
ED-METH	36.7 ± 0.22
AB-METH	37.7 ± 0.58**

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

** $p < 0.01$ in comparison with control group by ANOVA post hoc Dunnett test

Table 9 Effects of METH administration on locomotor activity in control and ED-METH groups on day 0-14

Group	Locomotor activity (squares crossed)							
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Control	90 ± 6.64	86 ± 13.35	90 ± 12.90	75 ± 13.03	73 ± 8.12	84 ± 14.71	56 ± 21.81	73 ± 16.83
ED-METH	70 ± 9.89	113 ± 14.70	135 ± 11.70*	141 ± 12.50**	122 ± 8.34**	142 ± 12.26**	150 ± 9.20***	193 ± 6.94***

Group	Locomotor activity (squares crossed)						
	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Control	80 ± 13.27	75 ± 25.22	67 ± 10.88	56 ± 16.70	56 ± 20.20	77 ± 19.06	56 ± 16.93
ED-METH	183 ± 8.67***	208 ± 7.40***	178 ± 7.06***	187 ± 7.15***	171 ± 6.11***	165 ± 6.99***	120 ± 7.25**

Note: Animals were treated with saline or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14. Data were presented as Mean ± SEM. ED-METH group (n = 8) and control group (n = 13).

* $p < 0.05$ in comparison with control group by t-test

** $p < 0.01$ in comparison with control group by t-test

*** $p < 0.001$ in comparison with control group by t-test

Table 10 Effects of escalating doses-METH binge administration on locomotor activity on day 15

Group	Squares crossed on day 15
Control	83.8 ± 14.10
ED-METH binge	127.0 ± 33.95
ED-METH	70.8 ± 20.58
AB-METH	2.2 ± 1.50**

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

** $p < 0.01$ in comparison with saline-treated group by ANOVA post hoc Dunnett test

Table 11 Expression of PCNA-IR in subgranular zone after escalating and binge doses-METH administration

Group	PCNA-IR cells in subgranular zone (% of control)
Control	100.00 ± 1.16
ED-METH binge	57.92 ± 0.57*
ED-METH	61.87 ± 1.35*
AB-METH	76.03 ± 2.26

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). At 24 h after the last injection, rats were sacrificed and brains were removed. The tissues sections were specific detected with mouse anti-PCNA and the immunodetected sections were investigated under a light microscope at 20x magnification. Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

* $p < 0.05$ in comparison with control group by ANOVA post hoc Dunnett test.

Table 12 Expression of PCNA-IR in subventricular zone after escalating and binge doses-METH administration

Group	PCNA-IR cells in subventricular zone (% of control)
Control	100.00 ± 1.36
ED-METH binge	69.78 ± 0.29 ^{***}
ED-METH	74.05 ± 0.41 ^{***}
AB-METH	84.30 ± 1.13 ^{**}

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). At 24 h after the last injection, rats were sacrificed and brains were removed. The tissues sections were specific detected with mouse anti-PCNA and the immunodetected sections were investigated under a light microscope at 20x magnification. Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

^{**} $p < 0.01$ in comparison with control group by ANOVA post hoc Dunnett test.

^{***} $p < 0.001$ in comparison with control group by ANOVA post hoc Dunnett test.

Table 13 Expression of MAP2-IR in subgranular zone after escalating and binge doses-METH administration

Group	MAP2-IR cells in subgranular zone (% of control)
Control	100.00 ± 1.44
ED-METH binge	29.64 ± 0.73 ^{***}
ED-METH	32.91 ± 1.28 ^{***}
AB-METH	80.43 ± 1.99

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). At 24 h after the last injection, rats were sacrificed and brains were removed. The tissues sections were specific detected with mouse anti-MAP2 and the immunodetected sections were investigated under a light microscope at 20x magnification. Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

^{***} $p < 0.001$ in comparison with control group by ANOVA post hoc Dunnett test.

Table 14 Expression of MAP2-IR in subventricular zone after escalating and binge doses-METH administration

Group	MAP2-IR cells in subventricular zone (% of control)
Control	100.00 ± 2.48
ED-METH binge	67.67 ± 2.99**
ED-METH	70.20 ± 0.76**
AB-METH	78.88 ± 1.29*

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). At 24 h after the last injection, rats were sacrificed and brains were removed. The tissues sections were specific detected with mouse anti-MAP2 and the immunodetected sections were investigated under a light microscope at 20x magnification. Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

* $p < 0.05$ in comparison with control group by ANOVA post hoc Dunnett test.

** $p < 0.01$ in comparison with control group by ANOVA post hoc Dunnett test.

Table 15 Expression of GFAP-IR cells in subgranular zone after escalating and binge doses-METH administration

Group	GFAP-IR cells in subgranular zone (% of control)
Control	100.00 ± 0.65
ED-METH binge	179.98 ± 1.18**
ED-METH	150.58 ± 2.81*
AB-METH	176.72 ± 2.44**

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). At 24 h after the last injection, rats were sacrificed and brains were removed. The tissues sections were specific detected with mouse anti-GFAP and the immunodetected sections were investigated under a light microscope at 20x magnification. Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

* $p < 0.05$ in comparison with control group by t-test.

** $p < 0.01$ in comparison with control group by ANOVA post hoc Dunnette test.

Table 16 Expression of GFAP-IR cells in subventricular zone after escalating and binge doses-METH administration

Group	GFAP-IR cells in subventricular zone (% of control)
Control	100.00 ± 2.28
ED-METH binge	127.42 ± 1.76*
ED-METH	113.78 ± 2.09
AB-METH	146.90 ± 1.80***

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). At 24 h after the last injection, rats were sacrificed and brains were removed. The tissues sections were specific detected with mouse anti-GFAP and the immunodetected sections were investigated under a light microscope at 20x magnification. Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

* $p < 0.05$ in comparison with control group by ANOVA post hoc Dunnett test.

*** $p < 0.001$ in comparison with control group by ANOVA post hoc Dunnett test.

Table 17 Expression of MBP-IR in cingulate cortex after escalating and binge doses-METH administration

Group	Optical density of MBP-IR in cingulate cortex (% of control)
Control	100.00 ± 17.33
ED-METH binge	56.60 ± 4.08*
ED-METH	66.80 ± 8.24
AB-METH	58.16 ± 7.40*

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). At 24 h after the last injection, rats were sacrificed and brains were removed. The tissues sections were specific detected with mouse anti-MBP and the immunodetected sections were investigated under a light microscope at 20x magnification. Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

* $p < 0.05$ in comparison with control group by ANOVA post hoc Dunnett test.

Table 18 Expression of MBP-IR in white matter after escalating and binge doses-METH administration

Group	Optical density of MBP-IR in white matter (% of control)
Control	100 ± 7.96
ED-METH binge	111.92 ± 3.79
ED-METH	96.29 ± 9.75
AB-METH	118.52 ± 5.33

Note: Animals were treated with saline (control) or saline on day 1-14 and 4x6.0 mg/kg METH at 2 h intervals on day 15 (AB-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and saline on day 15 (ED-METH) or gradually increasing three doses of METH (0.1-3.9 mg/kg/day) on day 1-13 and 3x4.0 mg/kg METH on day 14 and four consecutive injections of 6.0 mg/kg METH at 2 h intervals on day 15 (ED-METH binge). At 24 h after the last injection, rats were sacrificed and brains were removed. The tissues sections were specific detected with mouse anti-MBP and the immunodetected sections were investigated under a light microscope at 20x magnification. Data were presented as Mean ± SEM. ED-METH binge; escalating dose-methamphetamine binge group (n = 4), ED-METH; escalating dose-methamphetamine group (n = 4), AB-METH; acute dose-methamphetamine binge group (n = 5) and control group (n = 8)

Table 19 Effects of escalating and binge doses-METH administration on day 0-14

	ED-METH treated group vs. control group														
	Day														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Weight loss	x	0	0	--	-	--	0	--	--	---	---	--	---	---	---
Food intake	0	0	0	0	---	0	--	0	---	--	-	---	--	--	---
Behavioral test	0	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Locomotor activity	0	0	+	++	++	++	+++	+++	+++	+++	+++	+++	+++	+++	++

Note: 0, no effect; -, decrease; +, increase; x, no measure

Table 20 Effects of escalating and binge doses-METH administration on day 15 and day 16

Test	Group	Day 15	Day 16
Weight loss	ED-METH binge	---	x
	ED-METH	---	x
	AB-METH	0	x
Food intake	ED-METH binge	--	---
	ED-METH	--	0
	AB-METH	0	---
Core body temperature	ED-METH binge	0	x
	ED-METH	0	x
	AB-METH	++	x
Behavioral test	ED-METH binge	+++	x
	ED-METH	0	x
	AB-METH	+++	x
Locomotor activity	ED-METH binge	0	x
	ED-METH	0	x
	AB-METH	--	x

Note: 0, no effect; -, decrease; +, increase; x, no measure

Table 21 Effects of escalating and binge doses-METH administration on hippocampal neurogenesis in subgranular and subventricular zones

Neurogenesis	Marker	Area	Group	Expression
Proliferative cell	Proliferating cell nuclear antigen (PCNA)	SGZ	ED-METH binge	–
			ED-METH	–
			AB-METH	0
		SVZ	ED-METH binge	---
			ED-METH	---
			AB-METH	--
Mature neuron	Microtubule associated protein 2(MAP2)	SGZ	ED-METH binge	---
			ED-METH	---
			AB-METH	0
		SVZ	ED-METH binge	--
			ED-METH	--
			AB-METH	–
Astrocyte	Glial fibrillary acidic protein (GFAP)	SGZ	ED-METH binge	++
			ED-METH	+
			AB-METH	++
		SVZ	ED-METH binge	+
			ED-METH	0
			AB-METH	+++

Note: 0, no effect; –, decrease; +, increase; SGZ, subgranular zone; SVZ, subventricular zone

Table 21 Effects of escalating and binge doses-METH administration on hippocampal neurogenesis in subgranular and subventricular zones (CONT.)

Neurogenesis	Marker	Area	Group	Expression
Oligodendrocyte	Myelin basic protein (MBP)	Cingulate cortex	ED-METH binge	-
			ED-METH	0
			AB-METH	-
		White matter	ED-METH binge	0
			ED-METH	0
			AB-METH	0

Note: 0, no effect; -, decrease; +, increase; SGZ, subgranular zone; SVZ, subventricular zone