

**Table 1: Study design grouping**

<b>Number of group</b>	<b>Name group</b>	<b>Injections</b>
<b>Group 1</b>	Non-diabetic main control group	Normal saline ICV and subcutaneously (SC) in the left hind paw
<b>Group 2</b>	Non-diabetic control insulin group	Normal saline ICV and formalin SC in the left hind paw
<b>Group 3</b>	Non-diabetic control formalin test group	Insulin ICV and normal saline SC in the left hind paw
<b>Group 4</b>	Non-diabetic test group	Insulin ICV and formalin SC in the left hind paw
<b>Group 5</b>	Diabetic control insulin group	Normal saline ICV and formalin SC in the left hind paw
<b>Group 6</b>	Diabetic control formalin test group	Insulin ICV and normal saline in the left hind paw
<b>Group 7</b>	Diabetic test group	Insulin ICV and formalin SC in the left hind paw
<b>Group 8</b>	Diabetic main control group	Normal saline ICV and SC in the left hind paw

**Table 2: the concentration of norepinephrine (pg) in different groups (n=8, Mean ± SEM)**

Sample / Group	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8
<b>Group 1</b>	38.09 ± 1.39 <sup>a</sup>	37.34 ± 1.04 <sup>a</sup>	41.66 ± 1.51 <sup>a</sup>	34.24 ± 0.76 <sup>a</sup>	35.19 ± 0.72 <sup>a</sup>	35.20 ± 0.88 <sup>a</sup>	33.89 ± 1.22 <sup>a</sup>	30.37 ± 0.84 <sup>a</sup>
<b>Group 2</b>	36.21 ± 1.07 <sup>a</sup>	36.89 ± 1.02 <sup>a</sup>	87.33 ± 3.22 <sup>d</sup>	65.96 ± 2.23 <sup>c</sup>	59.07 ± 1.57 <sup>c</sup>	60.28 ± 1.39 <sup>c</sup>	59.22 ± 1.14 <sup>cd</sup>	60.10 ± 1.55 <sup>d</sup>
<b>Group 3</b>	37.93 ± 1.19 <sup>a</sup>	36.66 ± 1.27 <sup>a</sup>	44.84 ± 0.92 <sup>a</sup>	35.79 ± 1.03 <sup>a</sup>	35.62 ± 0.96 <sup>a</sup>	37.40 ± 1.12 <sup>a</sup>	35.91 ± 0.89 <sup>a</sup>	32.42 ± 0.68 <sup>ab</sup>
<b>Group 4</b>	36.44 ± 0.91 <sup>a</sup>	37.78 ± 1.06 <sup>a</sup>	105.24 ± 2.67 <sup>c</sup>	90.86 ± 2.10 <sup>d</sup>	76.56 ± 1.34 <sup>d</sup>	70.40 ± 1.22 <sup>d</sup>	61.18 ± 2.34 <sup>d</sup>	60.25 ± 0.58 <sup>d</sup>
<b>Group 5</b>	37.74 ± 1.10 <sup>a</sup>	36.88 ± 1.19 <sup>a</sup>	75.78 ± 1.12 <sup>c</sup>	64.14 ± 1.56 <sup>c</sup>	57.94 ± 1.16 <sup>bc</sup>	58.28 ± 1.36 <sup>bc</sup>	55.75 ± 0.96 <sup>bc</sup>	57.12 ± 1.58 <sup>cd</sup>
<b>Group 6</b>	38.27 ± 1.25 <sup>a</sup>	38.74 ± 1.16 <sup>a</sup>	42.15 ± 1.28 <sup>a</sup>	36.77 ± 0.99 <sup>a</sup>	37.61 ± 0.95 <sup>a</sup>	35.92 ± 1.17 <sup>a</sup>	36.52 ± 0.98 <sup>a</sup>	34.26 ± 1.04 <sup>b</sup>
<b>Group 7</b>	38.40 ± 1.13 <sup>a</sup>	38.86 ± 1.22 <sup>a</sup>	63.46 ± 1.94 <sup>b</sup>	53.01 ± 1.06 <sup>b</sup>	55.35 ± 1.23 <sup>b</sup>	55.20 ± 1.32 <sup>b</sup>	54.53 ± 1.45 <sup>b</sup>	55.27 ± 1.43 <sup>c</sup>
<b>Group 8</b>	39.27 ± 1.08 <sup>a</sup>	36.67 ± 1.10 <sup>a</sup>	43.81 ± 0.97 <sup>a</sup>	34.86 ± 1.16 <sup>a</sup>	36.45 ± 0.97 <sup>a</sup>	33.95 ± 1.04 <sup>a</sup>	35.82 ± 1.24 <sup>a</sup>	33.73 ± 1.02 <sup>ab</sup>

a, b, c, d Different small alphabetic letters show significant differences between groups

Group 1 (non-diabetic main control group) injected with normal saline ICV and subcutaneously (SC) in the left hind paw; group 2 (non-diabetic control insulin group) injected with normal saline ICV and formalin SC; group 3 (non-diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 4 (non-diabetic test group) injected with insulin ICV and formalin SC; group 5 (diabetic control insulin group) injected with normal saline ICV and formalin SC; group 6 (diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 7 (diabetic test group) injected with insulin ICV and formalin SC; group 8 (diabetic main control group) injected with normal saline ICV and SC. Sample numbers are according to collection of microdialysis samples every 15 min.[Base sample without medication effect (Sample1), Base sample with medication effect (Sample 2), four samples related to different times of the formalin test (Samples 3-6) and two samples after completion of formalin test (Samples 7, 8)].

**Table 3: the concentration of MHPG (pg) in different groups (n=8, Mean  $\pm$  SEM)**

Sample / Group	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8
<b>Group 1</b>	9.14 $\pm$ 0.69 <sup>a</sup>	8.97 $\pm$ 0.66 <sup>a</sup>	9.89 $\pm$ 0.51 <sup>a</sup>	8.74 $\pm$ 0.69 <sup>a</sup>	7.91 $\pm$ 0.80 <sup>a</sup>	6.91 $\pm$ 0.73 <sup>a</sup>	6.51 $\pm$ 0.77 <sup>a</sup>	5.77 $\pm$ 0.76 <sup>a</sup>
<b>Group 2</b>	9.12 $\pm$ 0.85 <sup>a</sup>	9.01 $\pm$ 0.83 <sup>a</sup>	17.16 $\pm$ 0.61 <sup>c</sup>	12.69 $\pm$ 0.58 <sup>b</sup>	11.52 $\pm$ 0.55 <sup>c</sup>	10.73 $\pm$ 0.60 <sup>c</sup>	10.06 $\pm$ 0.64 <sup>cd</sup>	9.68 $\pm$ 0.54 <sup>bc</sup>
<b>Group 3</b>	9.11 $\pm$ 0.82 <sup>a</sup>	9.17 $\pm$ 0.57 <sup>a</sup>	10.12 $\pm$ 0.46 <sup>a</sup>	9.09 $\pm$ 0.66 <sup>a</sup>	8.19 $\pm$ 0.60 <sup>ab</sup>	7.22 $\pm$ 0.61 <sup>ab</sup>	6.62 $\pm$ 0.86 <sup>a</sup>	5.78 $\pm$ 0.93 <sup>a</sup>
<b>Group 4</b>	9.01 $\pm$ 0.83 <sup>a</sup>	9.11 $\pm$ 0.82 <sup>a</sup>	20.47 $\pm$ 1 <sup>d</sup>	17.17 $\pm$ 0.64 <sup>c</sup>	15.03 $\pm$ 0.78 <sup>d</sup>	13.49 $\pm$ 0.60 <sup>d</sup>	11.59 $\pm$ 0.60 <sup>d</sup>	10.48 $\pm$ 0.59 <sup>c</sup>
<b>Group 5</b>	9.25 $\pm$ 0.56 <sup>a</sup>	9.17 $\pm$ 0.40 <sup>a</sup>	14.12 $\pm$ 0.79 <sup>b</sup>	11.95 $\pm$ 0.64 <sup>b</sup>	11.03 $\pm$ 0.59 <sup>c</sup>	10.06 $\pm$ 0.50 <sup>c</sup>	11.59 $\pm$ 0.60 <sup>bc</sup>	10.48 $\pm$ 0.59 <sup>bc</sup>
<b>Group 6</b>	9.29 $\pm$ 0.45 <sup>a</sup>	9.35 $\pm$ 0.56 <sup>a</sup>	10.54 $\pm$ 0.48 <sup>a</sup>	9.40 $\pm$ 0.51 <sup>a</sup>	8.49 $\pm$ 0.49 <sup>ab</sup>	7.59 $\pm$ 0.44 <sup>ab</sup>	9.18 $\pm$ 0.52 <sup>a</sup>	8.88 $\pm$ 0.53 <sup>a</sup>
<b>Group 7</b>	9.41 $\pm$ 0.35 <sup>a</sup>	9.35 $\pm$ 0.56 <sup>a</sup>	10.54 $\pm$ 0.48 <sup>a</sup>	9.40 $\pm$ 0.51 <sup>a</sup>	8.49 $\pm$ 0.49 <sup>bc</sup>	7.59 $\pm$ 0.44 <sup>bc</sup>	7.01 $\pm$ 0.55 <sup>ab</sup>	6.19 $\pm$ 0.57 <sup>b</sup>
<b>Group 8</b>	9.43 $\pm$ 0.58 <sup>a</sup>	9.23 $\pm$ 0.52 <sup>a</sup>	10.10 $\pm$ 0.57 <sup>a</sup>	9.16 $\pm$ 0.58 <sup>a</sup>	36.45 $\pm$ 0.97 <sup>ab</sup>	7.12 $\pm$ 0.59 <sup>a</sup>	6.93 $\pm$ 0.52 <sup>a</sup>	5.24 $\pm$ 0.47 <sup>a</sup>

<sup>a, b, c, d</sup> Different small alphabetic letters show significant differences between groups

Group 1 (non-diabetic main control group) injected with normal saline ICV and subcutaneously (SC) in the left hind paw; group 2 (non-diabetic control insulin group) injected with normal saline ICV and formalin SC; group 3 (non-diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 4 (non-diabetic test group) injected with insulin ICV and formalin SC; group 5 (diabetic control insulin group) injected with normal saline ICV and formalin SC; group 6 (diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 7 (diabetic test group) injected with insulin ICV and formalin SC; group 8 (diabetic main control group) injected with normal saline ICV and SC. Sample numbers are according to collection of microdialysis samples every 15 min. Base sample without medication effect (Sample1), Base sample with medication effect (Sample 2), four samples related to different times of the formalin test (Samples 3-6) and two samples after completion of formalin test (Samples 7, 8)].

**Table 4: the concentration of Dopamine (pg) in different groups (n=8, Mean  $\pm$  SEM)**

Sample / Group	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8
<b>Group 1</b>	1.31 $\pm$ 0.13 <sup>a</sup>	1.30 $\pm$ 0.09 <sup>a</sup>	1.90 $\pm$ 0.07 <sup>a</sup>	1.51 $\pm$ 0.10 <sup>a</sup>	1.60 $\pm$ 0.12 <sup>a</sup>	1.51 $\pm$ 0.12 <sup>a</sup>	1.49 $\pm$ 0.14 <sup>a</sup>	1.47 $\pm$ 0.11 <sup>a</sup>
<b>Group 2</b>	1.44 $\pm$ 0.10 <sup>a</sup>	1.35 $\pm$ 0.10 <sup>a</sup>	5.43 $\pm$ 0.94 <sup>c</sup>	4.29 $\pm$ 0.56 <sup>b</sup>	3.70 $\pm$ 0.48 <sup>b</sup>	3.43 $\pm$ 0.41 <sup>b</sup>	3.53 $\pm$ 0.52 <sup>bc</sup>	3.63 $\pm$ 0.54 <sup>bc</sup>
<b>Group 3</b>	1.35 $\pm$ 0.12 <sup>a</sup>	1.33 $\pm$ 0.08 <sup>a</sup>	2.01 $\pm$ 0.07 <sup>a</sup>	1.62 $\pm$ 0.20 <sup>a</sup>	1.66 $\pm$ 0.17 <sup>a</sup>	1.51 $\pm$ 0.11 <sup>a</sup>	1.54 $\pm$ 0.16 <sup>a</sup>	1.49 $\pm$ 0.15 <sup>a</sup>
<b>Group 4</b>	1.45 $\pm$ 0.16 <sup>a</sup>	1.41 $\pm$ 0.11 <sup>a</sup>	6.96 $\pm$ 0.62 <sup>d</sup>	5.77 $\pm$ 0.67 <sup>c</sup>	5.25 $\pm$ 0.65 <sup>c</sup>	4.51 $\pm$ 0.74 <sup>b</sup>	4.15 $\pm$ 0.73 <sup>c</sup>	3.93 $\pm$ 0.63 <sup>c</sup>
<b>Group 5</b>	1.50 $\pm$ 0.12 <sup>a</sup>	1.52 $\pm$ 0.12 <sup>a</sup>	4.17 $\pm$ 0.44 <sup>b</sup>	3.46 $\pm$ 0.36 <sup>b</sup>	3.18 $\pm$ 0.55 <sup>b</sup>	2.98 $\pm$ 0.37 <sup>ab</sup>	2.84 $\pm$ 0.36 <sup>b</sup>	2.97 $\pm$ 0.52 <sup>bc</sup>
<b>Group 6</b>	1.38 $\pm$ 0.10 <sup>a</sup>	1.39 $\pm$ 0.10 <sup>a</sup>	1.99 $\pm$ 0.12 <sup>a</sup>	1.82 $\pm$ 0.15 <sup>a</sup>	1.70 $\pm$ 0.14 <sup>a</sup>	1.54 $\pm$ 0.09 <sup>a</sup>	1.49 $\pm$ 0.17 <sup>a</sup>	1.47 $\pm$ 0.13 <sup>a</sup>
<b>Group 7</b>	1.52 $\pm$ 0.11 <sup>a</sup>	1.56 $\pm$ 0.01 <sup>a</sup>	2.89 $\pm$ 0.35 <sup>a</sup>	2.41 $\pm$ 0.33 <sup>a</sup>	2.64 $\pm$ 0.29 <sup>b</sup>	2.58 $\pm$ 1.25 <sup>b</sup>	2.60 $\pm$ 0.35 <sup>b</sup>	2.56 $\pm$ 0.36 <sup>a</sup>
<b>Group 8</b>	1.35 $\pm$ 0.08 <sup>a</sup>	1.32 $\pm$ 0.10 <sup>a</sup>	2.05 $\pm$ 0.14 <sup>a</sup>	1.73 $\pm$ 0.16 <sup>a</sup>	1.60 $\pm$ 0.13 <sup>a</sup>	1.60 $\pm$ 0.13 <sup>a</sup>	1.50 $\pm$ 0.11 <sup>a</sup>	1.51 $\pm$ 0.13 <sup>a</sup>

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Group 1 (non-diabetic main control group) injected with normal saline ICV and subcutaneously (SC) in the left hind paw; group 2 (non-diabetic control insulin group) injected with normal saline ICV and formalin SC; group 3 (non-diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 4 (non-diabetic test group) injected with insulin ICV and formalin SC; group 5 (diabetic control insulin group) injected with normal saline ICV and formalin SC; group 6 (diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 7 (diabetic test group) injected with insulin ICV and formalin SC; group 8 (diabetic main control group) injected with normal saline ICV and SC. Sample numbers are according to collection of microdialysis samples every 15 min .[Base sample without medication effect (Sample1), Base sample with medication effect (Sample 2), four samples related to different times of the formalin test (Samples 3-6) and two samples after completion of formalin test (Samples 7, 8)].

**Table 5: the concentration of DOPAC (pg) in different groups (n=8, Mean  $\pm$  SEM)**

Sample / Group	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8
<b>Group 1</b>	0.98 $\pm$ 0.04 <sup>a</sup>	0.95 $\pm$ 0.03 <sup>a</sup>	1.10 $\pm$ 0.05 <sup>a</sup>	0.97 $\pm$ 0.05 <sup>a</sup>	0.91 $\pm$ 0.04 <sup>a</sup>	0.86 $\pm$ 0.04 <sup>a</sup>	0.90 $\pm$ 0.05 <sup>a</sup>	0.79 $\pm$ 0.04 <sup>a</sup>
<b>Group 2</b>	0.95 $\pm$ 0.03 <sup>a</sup>	0.93 $\pm$ 0.04 <sup>a</sup>	3.06 $\pm$ 0.24 <sup>c</sup>	2.17 $\pm$ 0.28 <sup>b</sup>	1.68 $\pm$ 0.18 <sup>b</sup>	1.62 $\pm$ 0.18 <sup>cd</sup>	1.48 $\pm$ 0.17 <sup>bc</sup>	1.43 $\pm$ 0.18 <sup>cd</sup>
<b>Group 3</b>	0.96 $\pm$ 0.05 <sup>a</sup>	0.99 $\pm$ 0.05 <sup>a</sup>	1.13 $\pm$ 0.06 <sup>a</sup>	3.13 $\pm$ 0.05 <sup>a</sup>	0.99 $\pm$ 0.06 <sup>a</sup>	0.91 $\pm$ 0.05 <sup>ab</sup>	0.85 $\pm$ 0.05 <sup>a</sup>	0.81 $\pm$ 0.06 <sup>a</sup>
<b>Group 4</b>	0.94 $\pm$ 0.05 <sup>a</sup>	0.97 $\pm$ 0.05 <sup>a</sup>	4.02 $\pm$ 0.40 <sup>d</sup>	5.77 $\pm$ 0.34 <sup>c</sup>	2.60 $\pm$ 0.39 <sup>c</sup>	2.02 $\pm$ 0.32 <sup>d</sup>	1.79 $\pm$ 0.30 <sup>a</sup>	1.64 $\pm$ 0.34 <sup>d</sup>
<b>Group 5</b>	0.99 $\pm$ 0.05 <sup>a</sup>	0.96 $\pm$ 0.05 <sup>a</sup>	2.25 $\pm$ 0.23 <sup>b</sup>	1.81 $\pm$ 0.27 <sup>b</sup>	1.44 $\pm$ 0.23 <sup>ab</sup>	1.37 $\pm$ 0.20 <sup>bc</sup>	1.26 $\pm$ 0.17 <sup>c</sup>	1.29 $\pm$ 0.18 <sup>bcd</sup>
<b>Group 6</b>	1.01 $\pm$ 0.04 <sup>a</sup>	1.03 $\pm$ 0.04 <sup>a</sup>	1.20 $\pm$ 0.05 <sup>a</sup>	1.07 $\pm$ 0.05 <sup>a</sup>	0.95 $\pm$ 0.05 <sup>a</sup>	0.90 $\pm$ 0.05 <sup>ab</sup>	0.86 $\pm$ 0.06 <sup>a</sup>	0.91 $\pm$ 0.04 <sup>ab</sup>
<b>Group 7</b>	0.98 $\pm$ 0.05 <sup>a</sup>	0.99 $\pm$ 0.06 <sup>a</sup>	1.54 $\pm$ 0.22 <sup>a</sup>	1.23 $\pm$ 0.10 <sup>a</sup>	1.21 $\pm$ 0.18 <sup>a</sup>	1.11 $\pm$ 0.12 <sup>bc</sup>	1.14 $\pm$ 0.11 <sup>ab</sup>	1.03 $\pm$ 0.05 <sup>abc</sup>
<b>Group 8</b>	1 $\pm$ 0.04 <sup>a</sup>	0.97 $\pm$ 0.04 <sup>a</sup>	1.15 $\pm$ 0.04 <sup>a</sup>	0.99 $\pm$ 0.03 <sup>a</sup>	0.93 $\pm$ 0.04 <sup>a</sup>	0.94 $\pm$ 0.04 <sup>ab</sup>	0.88 $\pm$ 0.04 <sup>a</sup>	0.81 $\pm$ 0.04 <sup>a</sup>

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Group 1 (non-diabetic main control group) injected with normal saline ICV and subcutaneously (SC) in the left hind paw; group 2 (non-diabetic control insulin group) injected with normal saline ICV and formalin SC; group 3 (non-diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 4 (non-diabetic test group) injected with insulin ICV and formalin SC; group 5 (diabetic control insulin group) injected with normal saline ICV and formalin SC; group 6 (diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 7 (diabetic test group) injected with insulin ICV and formalin SC; group 8 (diabetic main control group) injected with normal saline ICV and SC. Sample numbers are according to collection of microdialysis samples every 15 min. Base sample without medication effect (Sample1), Base sample with medication effect (Sample 2), four samples related to different times of the formalin test (Samples 3-6) and two samples after completion of formalin test (Samples 7, 8)].

**Table 6: the concentration of Serotonin (pg) in different groups (n=8, Mean  $\pm$  SEM)**

Sample / Group	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8
<b>Group 1</b>	2.18 $\pm$ 0.27 <sup>a</sup>	2.27 $\pm$ 0.38 <sup>a</sup>	2.96 $\pm$ 0.36 <sup>a</sup>	2.66 $\pm$ 0.76 <sup>a</sup>	2.52 $\pm$ 0.19 <sup>a</sup>	2.42 $\pm$ 0.10 <sup>a</sup>	2.02 $\pm$ 0.10 <sup>a</sup>	2.10 $\pm$ 0.29 <sup>a</sup>
<b>Group 2</b>	2.25 $\pm$ 0.54 <sup>a</sup>	3.18 $\pm$ 0.79 <sup>a</sup>	7.88 $\pm$ 0.56 <sup>c</sup>	5.12 $\pm$ 0.36 <sup>b</sup>	4.01 $\pm$ 0.45 <sup>ab</sup>	3.60 $\pm$ 0.68 <sup>a</sup>	3.46 $\pm$ 0.26 <sup>bc</sup>	3.08 $\pm$ 0.44 <sup>abc</sup>
<b>Group 3</b>	2.31 $\pm$ 0.23 <sup>a</sup>	2.54 $\pm$ 0.51 <sup>a</sup>	2.98 $\pm$ 0.23 <sup>a</sup>	2.33 $\pm$ 0.26 <sup>a</sup>	2.77 $\pm$ 0.70 <sup>ab</sup>	2.70 $\pm$ 0.63 <sup>a</sup>	2.06 $\pm$ 0.27 <sup>a</sup>	2.20 $\pm$ 0.41 <sup>ab</sup>
<b>Group 4</b>	2.22 $\pm$ 0.23 <sup>a</sup>	3.11 $\pm$ 0.54 <sup>a</sup>	10.01 $\pm$ 0.87 <sup>d</sup>	1.44 $\pm$ 0.66 <sup>d</sup>	6 $\pm$ 0.42 <sup>d</sup>	5.19 $\pm$ 0.61 <sup>d</sup>	4.12 $\pm$ 0.41 <sup>c</sup>	3.84 $\pm$ 0.51 <sup>c</sup>
<b>Group 5</b>	2.43 $\pm$ 0.50 <sup>a</sup>	2.52 $\pm$ 0.48 <sup>a</sup>	5.59 $\pm$ 0.46 <sup>b</sup>	4.45 $\pm$ 0.43 <sup>b</sup>	4.22 $\pm$ 0.85 <sup>b</sup>	3.48 $\pm$ 0.79 <sup>a</sup>	3.01 $\pm$ 0.61 <sup>abc</sup>	3.02 $\pm$ 0.34 <sup>abc</sup>
<b>Group 6</b>	2.53 $\pm$ 0.38 <sup>a</sup>	2.64 $\pm$ 0.57 <sup>a</sup>	3.12 $\pm$ 0.53 <sup>a</sup>	2.60 $\pm$ 0.49 <sup>a</sup>	2.99 $\pm$ 0.42 <sup>ab</sup>	2.72 $\pm$ 0.24 <sup>a</sup>	2.37 $\pm$ 0.45 <sup>ab</sup>	2.34 $\pm$ 0.15 <sup>ab</sup>
<b>Group 7</b>	2.55 $\pm$ 0.56 <sup>a</sup>	2.83 $\pm$ 0.51 <sup>a</sup>	3.99 $\pm$ 0.49 <sup>a</sup>	3 $\pm$ 0.34 <sup>a</sup>	2.96 $\pm$ 0.26 <sup>ab</sup>	2.84 $\pm$ 0.26 <sup>a</sup>	2.81 $\pm$ 0.33 <sup>ab</sup>	3.26 $\pm$ 0.35 <sup>bc</sup>
<b>Group 8</b>	2.82 $\pm$ 0.32 <sup>a</sup>	2.38 $\pm$ 0.27 <sup>a</sup>	3.05 $\pm$ 0.36 <sup>a</sup>	2.99 $\pm$ 0.50 <sup>a</sup>	2.64 $\pm$ 0.32 <sup>ab</sup>	2.90 $\pm$ 0.55 <sup>a</sup>	2.50 $\pm$ 0.32 <sup>ab</sup>	2.59 $\pm$ 0.30 <sup>ab</sup>

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Group 1 (non-diabetic main control group) injected with normal saline ICV and subcutaneously (SC) in the left hind paw; group 2 (non-diabetic control insulin group) injected with normal saline ICV and formalin SC; group 3 (non-diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 4 (non-diabetic test group) injected with insulin ICV and formalin SC; group 5 (diabetic control insulin group) injected with normal saline ICV and formalin SC; group 6 (diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 7 (diabetic test group) injected with insulin ICV and formalin SC; group 8 (diabetic main control group) injected with normal saline ICV and SC. Sample numbers are according to collection of microdialysis samples every 15 min. Base sample without medication effect (Sample1), Base sample with medication effect (Sample 2), four samples related to different times of the formalin test (Samples 3-6) and two samples after completion of formalin test (Samples 7, 8)].

**Table 7: the concentration of HIAA (pg) in different groups (n=8, Mean  $\pm$  SEM)**

Sample / Group	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8
<b>Group 1</b>	0.72 $\pm$ 0.09 <sup>a</sup>	0.75 $\pm$ 0.13 <sup>a</sup>	0.98 $\pm$ 0.12 <sup>a</sup>	0.88 $\pm$ 0.25 <sup>a</sup>	0.84 $\pm$ 0.06 <sup>a</sup>	0.80 $\pm$ 0.03 <sup>a</sup>	0.67 $\pm$ 0.03 <sup>a</sup>	0.69 $\pm$ 0.10 <sup>a</sup>
<b>Group 2</b>	0.75 $\pm$ 0.18 <sup>a</sup>	1.06 $\pm$ 0.26 <sup>a</sup>	3.09 $\pm$ 0.45 <sup>c</sup>	2.16 $\pm$ 0.55 <sup>b</sup>	1.93 $\pm$ 0.43 <sup>b</sup>	1.24 $\pm$ 0.28 <sup>a</sup>	1.12 $\pm$ 0.23 <sup>ab</sup>	0.98 $\pm$ 0.17 <sup>ab</sup>
<b>Group 3</b>	0.77 $\pm$ 0.08 <sup>a</sup>	0.84 $\pm$ 0.17 <sup>a</sup>	0.99 $\pm$ 0.08 <sup>a</sup>	0.78 $\pm$ 0.09 <sup>a</sup>	0.89 $\pm$ 0.21 <sup>a</sup>	0.81 $\pm$ 0.20 <sup>a</sup>	0.68 $\pm$ 0.09 <sup>a</sup>	0.70 $\pm$ 0.14 <sup>a</sup>
<b>Group 4</b>	0.73 $\pm$ 0.08 <sup>a</sup>	1.03 $\pm$ 0.18 <sup>a</sup>	4.019 $\pm$ 0.50 <sup>d</sup>	3.22 $\pm$ 0.44 <sup>c</sup>	3.08 $\pm$ 0.58 <sup>c</sup>	2.17 $\pm$ 0.50 <sup>b</sup>	1.51 $\pm$ 0.30 <sup>b</sup>	1.36 $\pm$ 0.24 <sup>b</sup>
<b>Group 5</b>	0.81 $\pm$ 0.17 <sup>a</sup>	0.84 $\pm$ 0.16 <sup>a</sup>	2.14 $\pm$ 0.28 <sup>b</sup>	1.98 $\pm$ 0.49 <sup>b</sup>	1.44 $\pm$ 0.43 <sup>ab</sup>	1.05 $\pm$ 0.24 <sup>a</sup>	0.98 $\pm$ 0.20 <sup>a</sup>	0.91 $\pm$ 0.13 <sup>a</sup>
<b>Group 6</b>	0.84 $\pm$ 0.13 <sup>a</sup>	0.88 $\pm$ 0.19 <sup>a</sup>	1.04 $\pm$ 0.18 <sup>a</sup>	0.86 $\pm$ 0.16 <sup>ab</sup>	0.99 $\pm$ 0.14 <sup>a</sup>	0.90 $\pm$ 0.08 <sup>a</sup>	0.79 $\pm$ 0.15 <sup>a</sup>	0.78 $\pm$ 0.05 <sup>a</sup>
<b>Group 7</b>	0.85 $\pm$ 0.19 <sup>a</sup>	0.94 $\pm$ 0.17 <sup>a</sup>	1.29 $\pm$ 0.18 <sup>a</sup>	0.87 $\pm$ 0.15 <sup>ab</sup>	1.06 $\pm$ 0.14 <sup>a</sup>	0.94 $\pm$ 0.09 <sup>a</sup>	0.93 $\pm$ 0.11 <sup>a</sup>	0.91 $\pm$ 0.16 <sup>a</sup>
<b>Group 8</b>	0.89 $\pm$ 0.12 <sup>a</sup>	0.79 $\pm$ 0.09 <sup>a</sup>	1.01 $\pm$ 0.12 <sup>a</sup>	0.91 $\pm$ 0.17 <sup>a</sup>	0.93 $\pm$ 0.11 <sup>a</sup>	0.86 $\pm$ 0.21 <sup>a</sup>	0.86 $\pm$ 0.10 <sup>a</sup>	0.79 $\pm$ 0.12 <sup>a</sup>

a, b, c, d Different small alphabetic letters show significant differences between groups

Group 1 (non-diabetic main control group) injected with normal saline ICV and subcutaneously (SC) in the left hind paw; group 2 (non-diabetic control insulin group) injected with normal saline ICV and formalin SC; group 3 (non-diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 4 (non-diabetic test group) injected with insulin ICV and formalin SC; group 5 (diabetic control insulin group) injected with normal saline ICV and formalin SC; group 6 (diabetic control formalin test group) injected with insulin ICV and normal saline SC; group 7 (diabetic test group) injected with insulin ICV and formalin SC; group 8 (diabetic main control group) injected with normal saline ICV and SC. Sample numbers are according to collection of microdialysis samples every 15 min. Base sample without medication effect (Sample1), Base sample with medication effect (Sample 2), four samples related to different times of the formalin test (Samples 3-6) and two samples after completion of formalin test (Samples 7, 8)].