

**Supplementary Table S1.** Effect of control, electrical stimulation tooth pulp, and URB597 on the levels of SP, CGRP, and EM-2 mRNAs in mesencephalon, thalamus, and hypothalamus in rats. SP, CGRP and EM-2 mRNA levels are shown as relative quantity ( $2^{\Delta\Delta C_t}$ )  $\pm$  SEM.

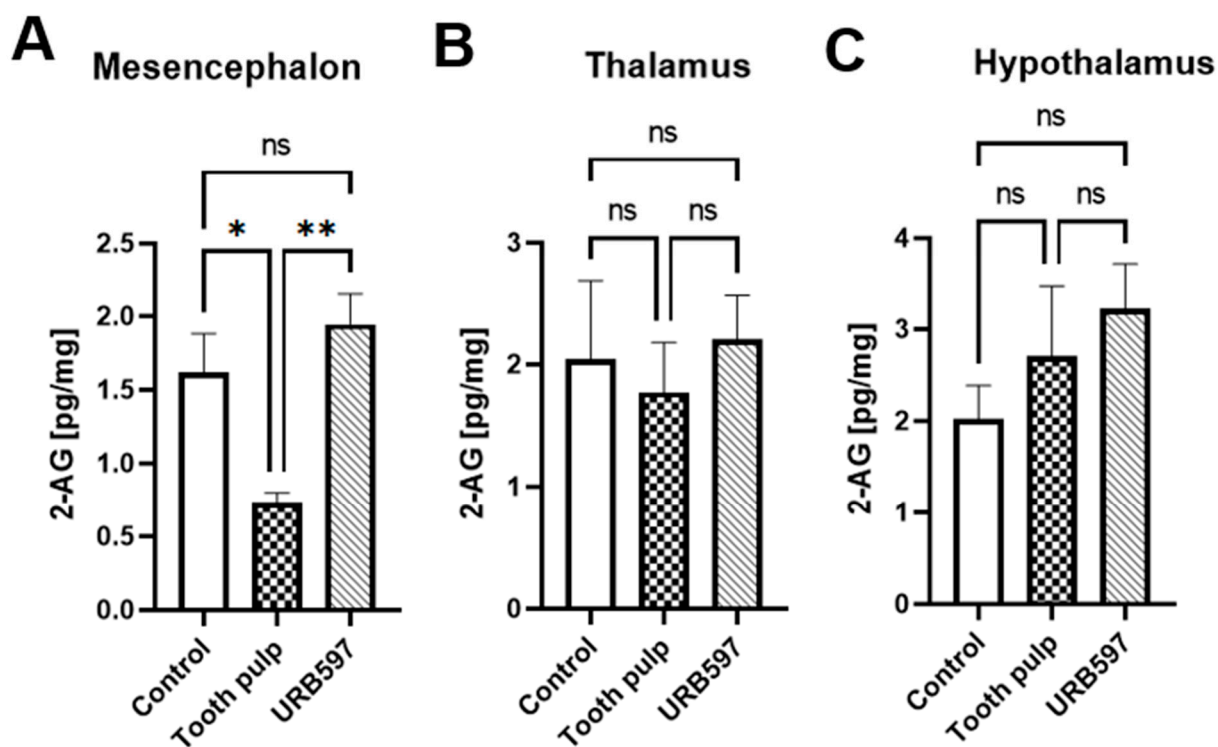
Signaling mediators	Brain structure	Control	Tooth pulp	URB597	Control vs. Tooth pulp <i>p</i> - value	Control vs. URB597 <i>p</i> - value	Tooth pulp vs. URB597 <i>p</i> - value
SP	mesencephalon	0.3488 $\pm$ 0.0371	0.7007 $\pm$ 0.0101	0.2702 $\pm$ 0.0282	<0.0001	0.1415	<0.0001
	thalamus	0.0052 $\pm$ 0.0005	0.0068 $\pm$ 0.0006	0.0043 $\pm$ 0.0004	0.0819	0.4907	0.0086
	hypothalamus	0.3103 $\pm$ 0.0260	0.5847 $\pm$ 0.0310	0.1842 $\pm$ 0.0286	<0.0001	0.0182	<0.0001
CGRP	mesencephalon	0.2553 $\pm$ 0.0049	0.7040 $\pm$ 0.0056	0.1443 $\pm$ 0.0203	<0.0001	<0.0001	<0.0001
	thalamus	0.1445 $\pm$ 0.0051	0.2775 $\pm$ 0.0056	0.1308 $\pm$ 0.0044	<0.0001	0.1736	<0.0001
	hypothalamus	0.3153 $\pm$ 0.0018	0.7588 $\pm$ 0.0142	0.2043 $\pm$ 0.0226	<0.0001	0.0004	<0.0001
EM-2	mesencephalon	0.1193 $\pm$ 0.0034	0.2228 $\pm$ 0.0026	0.1178 $\pm$ 0.0049	<0.0001	0.9571	<0.0001
	thalamus	0.3710 $\pm$ 0.0015	0.5138 $\pm$ 0.0071	0.3367 $\pm$ 0.0025	<0.0001	0.0002	<0.0001
	hypothalamus	0.2372 $\pm$ 0.0117	0.4065 $\pm$ 0.0054	0.1803 $\pm$ 0.0223	<0.0001	0.0406	<0.0001

**Supplementary Table S2.** Effect of control, electrical stimulation tooth pulp, and URB597 on the CB1, CB2, and MOR mRNA expression levels in rat mesencephalon, thalamus, and hypothalamus. Data are presented as relative quantity ( $2^{\Delta\Delta C_t}$ )  $\pm$  SEM.

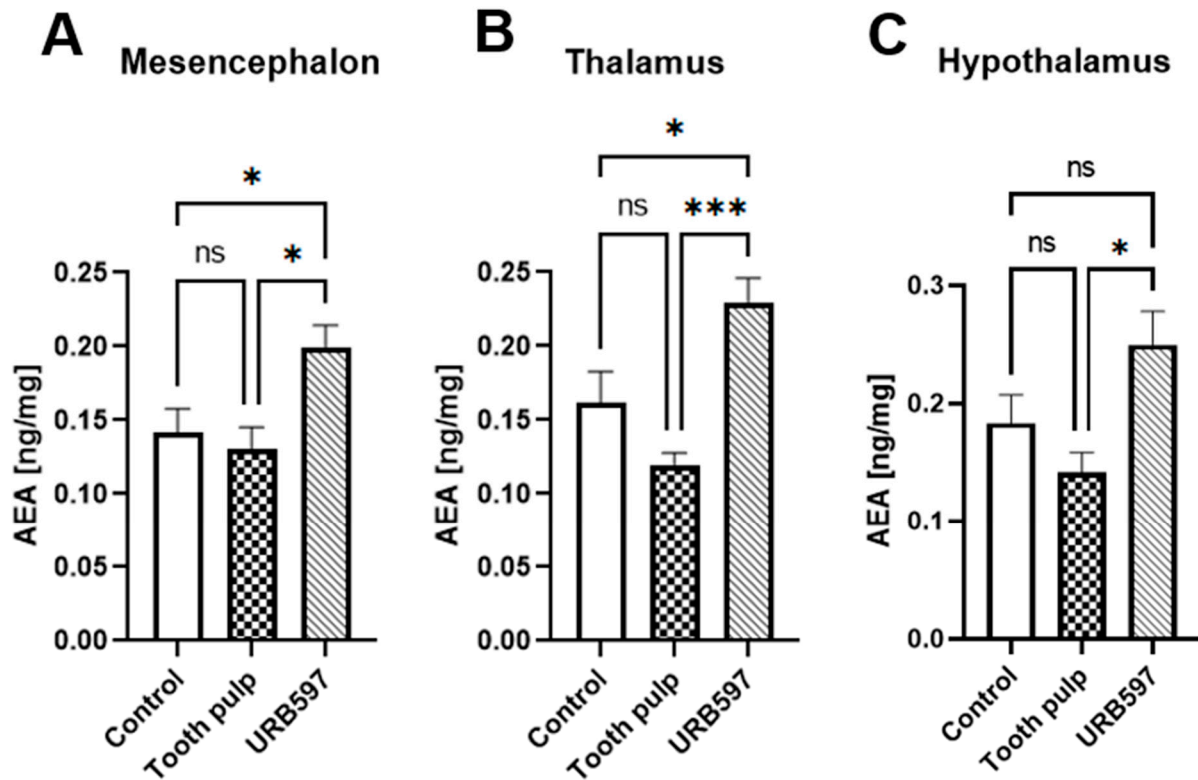
Receptors	Brain structure	Control	Tooth pulp	URB597	Control vs Tooth pulp <i>p</i> - value	Control vs URB597 <i>p</i> - value	Tooth pulp vs URB597 <i>p</i> - value
CB1R	mesencephalon	0.1678 $\pm$ 0.0104	0.1678 $\pm$ 0.0096	0.2258 $\pm$ 0.0163	>0.9999	0.0129	0.0129
	thalamus	0.1147 $\pm$ 0.0117	0.1103 $\pm$ 0.0161	0.1703 $\pm$ 0.0149	0.9753	0.0382	0.0253
	hypothalamus	0.2045 $\pm$ 0.0224	0.1640 $\pm$ 0.0114	0.2552 $\pm$ 0.0211	0.3132	0.1751	0.0103
CB2R	mesencephalon	0.1425 $\pm$ 0.0045	0.1343 $\pm$ 0.0034	0.1285 $\pm$ 0.0206	0.8866	0.7061	0.9402
	thalamus	0.1315 $\pm$ 0.0043	0.1252 $\pm$ 0.0048	0.1132 $\pm$ 0.0062	0.6676	0.0585	0.2580
	hypothalamus	0.1922 $\pm$ 0.0043	0.1652 $\pm$ 0.0172	0.1337 $\pm$ 0.0091	0.2543	0.0072	0.1644
MOR	mesencephalon	0.2358 $\pm$ 0.0035	0.3843 $\pm$ 0.0153	0.1715 $\pm$ 0.0080	<0.0001	0.0012	<0.0001
	thalamus	0.1258 $\pm$ 0.0181	0.1722 $\pm$ 0.0188	0.0617 $\pm$ 0.0115	0.1483	0.0367	0.0007
	hypothalamus	0.0522 $\pm$ 0.0068	0.0873 $\pm$ 0.0045	0.0343 $\pm$ 0.0048	0.0010	0.0846	<0.0001

**Supplementary Table S3.** Effect of control, electrical stimulation tooth pulp, and URB597 on the levels of AEA and 2-AG in mesencephalon, thalamus and hypothalamus in rats. AEA and 2-AG are presented as normalized concentration [pmol/g]  $\pm$  SEM.

Signaling endocannabinoids	Brain structure	Control	Tooth pulp	URB597	Control vs. Tooth pulp <i>p</i> - value	Control vs. URB597 <i>p</i> - value	Tooth pulp vs. URB597 <i>p</i> - value
AEA	mesencephalon	24.56 $\pm$ 2.52	22.34 $\pm$ 3.98	39.56 $\pm$ 3.33	0.8854	0.0159	0.0062
	thalamus	34.12 $\pm$ 4.55	24.20 $\pm$ 3.07	51.61 $\pm$ 4.81	0.2505	0.0261	0.0010
	hypothalamus	38.95 $\pm$ 4.93	32.47 $\pm$ 4.22	58.08 $\pm$ 6.22	0.6586	0.0490	0.0087
2-AG	mesencephalon	0.2450 $\pm$ 0.0466	0.1150 $\pm$ 0.0118	0.3083 $\pm$ 0.0409	0.0574	0.4547	0.0051
	thalamus	0.2533 $\pm$ 0.1117	0.3633 $\pm$ 0.0820	0.4450 $\pm$ 0.0593	0.6524	0.2938	0.7877
	hypothalamus	0.4500 $\pm$ 0.1131	0.5817 $\pm$ 0.0734	0.3967 $\pm$ 0.0823	0.5757	0.9106	0.3493



**Supplementary Figure S1.** 2-AG concentration normalized to milligram of total protein concentration in weighed tissue in controls and after tooth pulp and URB597 treatment. The data represent mean  $\pm$  SEM of 6 rats per group. Statistical significance was assessed using one-way ANOVA and a post-hoc multiple comparison Tukey test. Asterisks denote significance level (\* <0.05, \*\*<0.01, \*\*\* <0.001, \*\*\*\* <0.0001, ns- not statistically significant).



**Supplementary Figure S2.** AEA concentration normalized to milligram of total protein concentration in weighed tissue in controls and after tooth pulp and URB597 treatment. The data represent mean  $\pm$  SEM of 6 rats per group. Statistical significance was assessed using one-way ANOVA and a post-hoc multiple comparison Tukey test. Asterisks denote significance level (\* <0.05, \*\*<0.01, \*\*\* <0.001, \*\*\*\* <0.0001, ns- not statistically significant).