

Supplementary Table 1. Pharmacological manipulation of the Diffuse Noxious Inhibitory Controls circuitry. Listed by year and first author.

PMID	FIRST AUTHOR	YEAR	ANIMAL	CONDITION	DRUG	INJECTION SITE	DOSE	ANAESTH.	READOUT	TESTING STIMULUS	COND. STIMULUS	READOUT PLACE	TARGETED SYSTEM	DNIC EXPRESSION BEFORE DRUG	DNIC EXPRESSION AFTER DRUG	COMMENT
646457	Dickenson AH	1981	Rat ( $\delta$ , SD)	Naive	P-chlorophenylalanine	Systemic (i.p.)	300 mg/kg/day (3 days)	Halothane	Eph	Electrical	Thermal Mechanical Chemical	Spinal WDR	Executive system	Expressed	Not expressed	P-chlorophenylalanine: irreversible inhibitor of tryptophan hydroxylase (serotonin depletion)
726590	Le Bars D	1981	Rat ( $\delta$ , SD)	Naive	Morphine	Systemic (i.v.)	0.01 mg/kg 0.1 mg/kg 1 mg/kg 2 mg/kg	Halothane	Eph	Electrical	Thermal Mechanical	Spinal WDR	Systemic	Expressed	Not expressed	Morphine: $\mu$ -opioid receptor agonist (MOR) Naloxone: Opioid receptor antagonist
					Naloxone	Systemic (i.v.)	0.1-0.2 mg/kg 0.2-0.4 mg/kg						Systemic	Expressed	Expressed	
6260285	Kraus E	1981	Rat ( $\delta$ , SD)	Naive	Naloxone	Systemic (i.v.)	40 mg/kg 100 mg/kg 200 mg/kg	N/A	Beh	Electrical	Chemical	Vocalization	Systemic	Expressed	Not expressed	Naloxone: Opoid receptor antagonist
6257327	Le Bars D	1981	Rat ( $\delta$ , SD)	Naive	Naloxone	Systemic (i.v.)	0.3 mg/kg	Halothane	Eph	Electrical	Thermal	Spinal WDR	Systemic	Expressed	Not expressed	Naloxone: Opoid receptor antagonist
678166	Chitour D	1982	Rat ( $\delta$ , SD)	Naive	Cisnerin	Systemic (i.v.)	4 mg/kg	Halothane	Eph	Electrical	Thermal Mechanical	Spinal WDR	Systemic	Expressed	Not expressed	Cisnerin: S-HT2A and S-HT2C receptor antagonist Metergoline: 5-HT2A and 5-HT2C receptor antagonist S-hydroxytryptophan: Serotonin precursor
					Metergoline	Systemic (i.v.)	5 mg/kg						Systemic	Expressed	Not expressed	
					S-hydroxytryptophan	Systemic (i.v.)	30 mg/kg						Systemic	Expressed	Expressed [enhanced]	
676820	Kraus E	1982	Rat ( $\delta$ , SD)	Naive	S-hydroxytryptophan	Systemic (i.p.)	5.55 mg/kg 15.5 mg/kg 45 mg/kg	N/A	Beh	Electrical	Chemical	Vocalization	Systemic	Expressed	Expressed [enhanced]	S-hydroxytryptophan: Serotonin precursor Cisnerin: S-HT2A and S-HT2C receptor antagonist
					Cisnerin	Systemic (i.p.)	20 mg/kg						Systemic	Expressed	Expressed [enhanced]	
					S-hydroxytryptophan + Cisnerin	Systemic (i.p.)	50 mg/kg + 10 mg/kg						Systemic	Expressed	Expressed	
6626970	Cadden SW	1983	Rat ( $\delta$ , SD)	Naive	Xylocaine	Infusion (C2)	25 $\mu$ l (5%)	Halothane	Eph	Mechanical	Thermal Mechanical	Spinal WDR	Descending system (NO TABLE)	Expressed	Not expressed	Xylocaine: Voltage-gated sodium channel blocker
6664236	Dickenson AH	1983	Rat ( $\delta$ , ??)	Naive	Morphine	Microinjection med-rostral periarticular grey (PAG)	5 $\mu$ g in 0.2 $\mu$ l	Halothane	Eph	Electrical	Thermal	Spinal WDR	Top-down system	Expressed	Not expressed	Morphine: $\mu$ -opioid receptor agonist (MOR)
2986269	Villanueva L	1985	Rat ( $\delta$ , SD)	Naive	ES 52	Systemic (i.v.)	10 mg/kg	Halothane	Eph	Electrical	Thermal	Spinal WDR	Systemic	Expressed	Expressed	ES 52: inhibitor of enkephaline (derivative of $\delta$ -thiophane)
3763236	Villanueva L	1986	Rat ( $\delta$ , ??)	Naive	Morphine sulfate	Intrathecal (i.th.)	150 $\mu$ g in 20 $\mu$ l	Halothane	Eph	Electrical	Thermal	Medullary WDR	Ascending TS or CS	Expressed (tail)	Not expressed (tail)	Morphine: $\mu$ -opioid receptor agonist (MOR) Naloxone: Opioid receptor antagonist
					Naloxone	Systemic (i.v.)	0.4 mg/kg						Ascending TS or CS	Expressed	Expressed	
					Morphine sulphate	Intracerebroventricular (i.c.v.)	0.01 $\mu$ l + 2 $\mu$ l 1.25 $\mu$ l + 2 $\mu$ l 2.5 $\mu$ l + 2 $\mu$ l 10 $\mu$ l + 2 $\mu$ l 40 $\mu$ l + 2 $\mu$ l						Systemic	Expressed	Not expressed	Morphine: $\mu$ -opioid receptor agonist (MOR) Naloxone: Opioid receptor antagonist
3171978	Bouhassira D	1988	Rat ( $\delta$ , SD)	Naive	Morphine base	Intracerebroventricular (i.c.v.)	10 $\mu$ g in 2 $\mu$ l	Halothane	Eph	Electrical	Thermal	Spinal WDR	Systemic	Expressed	Not expressed	Morphine: $\mu$ -opioid receptor agonist (MOR) Naloxone: Opioid receptor antagonist
3378576	Bouhassira D	1988	Rat ( $\delta$ , SD)	Naive	Naloxone	Systemic (i.v.)	0.4 mg/kg	Halothane	Eph	Electrical	Thermal	Spinal WDR	Systemic	Expressed	Expressed	Morphine: $\mu$ -opioid receptor agonist (MOR) Naloxone: Opioid receptor antagonist
2247225	Bing Z	1990	Rat ( $\delta$ , SD)	Naive	Naloxone	Systemic (i.v.)	0.4 mg/kg	Halothane	Eph	Electrical	Thermal Mechanical	Medullary WDR	Systemic	Expressed	Not expressed	Naloxone: Opioid receptor antagonist
1397003	Bouhassira D	1992	Rat ( $\delta$ , SD)	Naive	Morphine chloride	Systemic (i.v.)	1 mg/kg	Halothane	Eph	Electrical	Thermal	Spinal WDR	Systemic	Expressed	Not expressed	Morphine: $\mu$ -opioid receptor agonist (MOR) Naloxone: Opioid receptor antagonist
					Naloxone	Systemic (i.v.)	0.4 mg/kg						Systemic	Expressed	Expressed	
					Periaqueductal grey (PAG) lesion	Morphine chloride	Systemic (i.v.)						Systemic	Expressed	Expressed	
8750730	Guirland F	1995	Rat ( $\gamma$ , SD)	Naive	Buprenorphine hydrochloride	Systemic (i.v.)	0.1 mg/kg 1 mg/kg 2 mg/kg 4 mg/kg	Halothane	EMG	Electrical	Thermal	Biceps femoris muscle	Systemic	Expressed	Not expressed	Buprenorphine: Partial $\mu$ -opioid receptor (MOR) agonist
8973815	Okada K	1996	Rat ( $\gamma$ , SD)	Naive	Capsaicin	Sciatic nerve (cotton ball)	1.5%	Thiamylal sodium	EMG	Electrical	Thermal Mechanical	Jaw opening-reflex (JOR)	Ascending TS or CS	Expressed	Not expressed	Capsaicin: TRPV1 agonist
9729390	Dualé C	1998	Rat ( $\delta$ , SD)	Naive	Morphine hydrochloride	Microinjection nucleus raphe magnus (NRM)	2.5 $\mu$ g in 0.2 $\mu$ l 5 $\mu$ g in 0.5 $\mu$ l	Halothane	Eph	Electrical	Thermal	Medullary WDR	Top-down system	Expressed	Expressed	Morphine: $\mu$ -opioid receptor agonist (MOR)
12818952	Jinks SL	2003	Rat ( $\delta$ , SD)	Naive	Isoflurane	Gaseous (inhaled)	0.3 MAC 1.2 MAC	Isoflurane	Eph	Mechanical	Spinal WDR	Systemic	Expressed	Expressed (0.8 MAC)	Isoflurane: General anaesthetic MAC: Minimum alveolar anaesthetic concentration necessary to produce immobility to a noxious stimulus	
1969715	Sanada T	2009	Rat ( $\delta$ , W)	Naive	Dexamethomidine hydrochloride	Systemic (i.v.)	0.4 $\mu$ g/kg + 1 $\mu$ l/min 0.5 $\mu$ g/kg + until end	Sevoflurane	EMG	Electrical	Thermal	Biceps femoris muscle	Systemic	Expressed	Not expressed	Dexamethomidine: $\alpha$ 2-adrenoceptor agonist Phenylephrine: $\alpha$ 1-adrenoceptor agonist Alpametole: $\alpha$ 1-adrenoceptor antagonist Phentolamine mesylate: $\alpha$ 2/ $\alpha$ 1-adrenoceptor antagonist
					Phenylephrine	Systemic (i.v.)	5 $\mu$ g/kg/min (10 min)						Systemic	Expressed	Not expressed	
					Alpametole hydrochloride	Systemic (i.m.)	0.5 mg/kg						Systemic	Expressed	Expressed	
					Phentolamine mesylate	Systemic (i.m.)	0.1 mg/kg						Systemic	Expressed	Expressed	
15331081	Lapost O	2009	Rat ( $\delta$ , SD)	Naive	RP67581	Intrathecal (i.th.)	NOT STATED (probably 20 $\mu$ g in 10 $\mu$ l)	N/A	Beh	Chemical	Facial grooming	Ascending TS or CS	Expressed	Expressed	RP67581: NK1R inactive antagonist Muscimol: GABA A-agonist	
					RP67580	Intrathecal (i.th.)	20 $\mu$ g in 10 $\mu$ l						Ascending TS or CS	Expressed	Not expressed	
					Muscimol	Microinjection left parabrachial area (PBL)	0.25 nmol in 100 nl	Halothane	Eph	Electrical	Thermal	Medullary WDR	Ascending TS or CS	Expressed	Not expressed	
2036698	Okada-Ogawa A	2009	Rat ( $\delta$ , SD)	Naive	Morphine sulfate	Subcutaneous pellets	75 mg (x2)	Urethane	Eph	Thermal	Chemical	Facial grooming	Systemic	Expressed	Expressed	Morphine: $\mu$ -opioid receptor agonist (MOR) Urethane: Voltage-gated sodium channel blocker
					Subcutaneous osmotic mini-pumps	1 $\mu$ l (64 mg/ml)	Systemic						Expressed	Not expressed		
					Urodecan	Microinjection rostral ventromedial medulla (RVMM)										

Supplementary Table 2. DNIC expression after systemic drug application. Listed by the drug.

PMID	CONDITION	DRUG	INJECTION SITE	ANAESTHESIA	READOUT	DNIC EXPRESSION BEFORE DRUG	DNIC EXPRESSION AFTER DRUG	PHARMACOLOGY
6260285	Naïve	Naloxone	Systemic (i.v.)	N/A	Beh	Expressed	Not expressed	Opioid receptor antagonist
6257327	Naïve	Naloxone	Systemic (i.v.)	Halothane	Eph	Expressed	Not expressed	Opioid receptor antagonist
2247225	Naïve	Naloxone	Systemic (i.v.)	Halothane	Eph	Expressed	Not expressed	Opioid receptor antagonist
27178898	Naïve	Naloxone	Systemic (i.p.)	N/A	Beh	Expressed	Not expressed	Opioid receptor antagonist
20302612	Naïve	Naloxone	Systemic (i.p.)	Halothane	Beh	Expressed	Not expressed	Opioid receptor antagonist
21330219	Muscle inflammation	Naloxone	Systemic (s.c.)	N/A	Beh	Expressed	Not expressed	Opioid receptor antagonist
27178898	Naïve	Naloxone	Intracerebroventricular (i.c.v.)	N/A	Beh	Expressed	Not expressed	Opioid receptor antagonist
7260590	Naïve	Morphine + Naloxone	Systemic (i.v.) + Systemic (i.v.)	Halothane	Eph	Expressed	Expressed	MOR-DOR agonist + opioid receptor antagonist
3171978	Naïve	Morphine + Naloxone	i.c.v. + Systemic (i.v.)	Halothane	Eph	Expressed	Expressed	MOR-DOR agonist + opioid receptor antagonist
3378576	Naïve	Morphine + Naloxone	i.c.v. + Systemic (i.v.)	Halothane	Eph	Expressed	Expressed	MOR-DOR agonist + opioid receptor antagonist
1397003	Naïve	Morphine + Naloxone	Systemic (i.v.) + Systemic (i.v.)	Halothane	Eph	Expressed	Expressed	MOR-DOR agonist + opioid receptor antagonist
23843537	Naïve	Naloxone + DAMGO	Systemic (i.v.) + i.th.	Halothane	Eph	Expressed	Expressed	Opioid receptor antagonist + MOR agonist
23843537	Naïve	Deltorindole + Deltorphin II	Systemic (i.v.) + i.th.	Halothane	Eph	Expressed	Expressed	DOR antagonist + DOR agonist
7260590	Naïve	Morphine	Systemic (i.v.)	Halothane	Eph	Expressed	Not expressed	MOR-DOR agonist
1397003	Naïve	Morphine	Systemic (i.v.)	Halothane	Eph	Expressed	Not expressed	MOR-DOR agonist
1397003	PAG lesion	Morphine	Systemic (i.v.)	Halothane	Eph	Expressed	Expressed	MOR-DOR agonist
20016098	Naïve	Morphine sulfate	Subcutaneous pellets	Urethane	Eph	Expressed	Not expressed	MOR-DOR agonist
20016098	Naïve	Morphine sulfate	Subcutaneous osmotic minipumps	Urethane	Eph	Expressed	Not expressed	MOR-DOR agonist
21929659	Naïve	Morphine sulfate	Subcutaneous pellets	Urethane	IHC	Expressed	Not expressed	MOR-DOR agonist
29369967	Naïve	Morphine sulfate	Subcutaneous osmotic minipumps	N/A	Beh	Expressed	Expressed	MOR-DOR agonist
30286616	Naïve	Morphine sulfate	Subcutaneous osmotic minipumps	N/A	Beh	Expressed	Not expressed	MOR-DOR agonist
3171978	Naïve	Morphine sulphate	Intracerebroventricular (i.c.v.)	Halothane	Eph	Expressed	Not expressed	MOR-DOR agonist
3378576	Naïve	Morphine base	Intracerebroventricular (i.c.v.)	Halothane	Eph	Expressed	Not expressed	MOR-DOR agonist
29369967	BLS	nor-binaltorphimine	Systemic (s.c.)	N/A	Beh	Not expressed	Expressed	MOR agonist
30870321	SNL	Nor-binaltorphimine	Systemic (s.c.)	N/A	Beh	Not expressed	Expressed	KOR antagonist
2986769	Naïve	ES 52	Systemic (i.v.)	Halothane	Eph	Expressed	Expressed	Inhibitor of enkephalinase (derivative of Thiorphan)
8750730	Naïve	Buprenorphine hydrochloride	Systemic (i.v.)	Halothane	EMG	Expressed	Not expressed	Partial MOR agonist
26010460	SNL	Tapentadol	Systemic (s.c.)	Isoflurane	Eph	Not expressed	Expressed	NRI and MOR agonist
30821870	OA-MIA (late stage)	Tapentadol	Systemic (s.c.)	Isoflurane	Eph	Not expressed	Expressed	NRI and MOR agonist
30461363	OA-MIA (late stage)	Tapentadol	Systemic (s.c.)	Isoflurane	Eph	Not expressed	Expressed	NRI and MOR agonist
30821870	OA-MIA (late stage)	Tapentadol + Pregabalin	Systemic (s.c.)	Isoflurane	Eph	Not expressed	Expressed	NRI and MOR agonist + See below
30821870	OA-MIA (late stage)	Pregabalin	Systemic (s.c.)	Isoflurane	Eph	Not expressed	Not expressed	Blocker of voltage-gated calcium channels (VGCCs) that inhibits neurotransmitter release
32315711	PSNL	Pregabalin	Orally administered (p.o.)	N/A	Beh	Not expressed	Not expressed	
32315711	OA-MIA (late stage)	Pregabalin	Orally administered (p.o.)	N/A	Beh	Not expressed	Not expressed	
26010460	SNL	Yohimbine	Systemic (s.c.)	Isoflurane	Eph	Not expressed	Not expressed	$\alpha_2$ -adrenoceptor antagonist
32745472	Naïve	Atipamezole hydrochloride	Systemic (s.c.)	N/A	Beh	Expressed	Not expressed	$\alpha_2$ -adrenoceptor antagonist
19697515	Naïve	Atipamezole hydrochloride + Dexmedetomidine hydrochloride	Systemic (i.m.) + Systemic (i.v.)	Sevoflurane	EMG	Expressed	Expressed	$\alpha_2$ -adrenoceptor antagonist + $\alpha_2$ -adrenoceptor agonist
19697515	Naïve	Phentolamine mesylate + Phenylephrine	Contralateral biceps femoris (i.m.)	Sevoflurane	EMG	Expressed	Expressed	$\alpha_{1/2}$ -adrenoceptor antagonist + $\alpha_1$ -adrenoceptor agonist
28700539	Migraine model	Propranolol	Oral gavage	Halothane	Eph	Not expressed	Expressed	Non-selective $\beta$ -adrenoceptor antagonist
19697515	Naïve	Dexmedetomidine hydrochloride	Systemic (i.v.)	Sevoflurane	EMG	Expressed	Not expressed	$\alpha_2$ -adrenoceptor agonist
19697515	Naïve	Phenylephrine	Systemic (i.v.)	Sevoflurane	EMG	Expressed	Not expressed	$\alpha_1$ -adrenoceptor agonist
6978166	Naïve	Metergoline	Systemic (i.v.)	Halothane	Eph	Expressed	Not expressed	5-HT <sub>1<math>\alpha</math></sub> , 5-HT <sub>2</sub> and 5-HT <sub>3</sub> receptor antagonist
6976820	Naïve	Cinanserin	Systemic (i.p.)	N/A	Beh	Expressed	Expressed	5-HT <sub>2A</sub> and 5-HT <sub>2C</sub> receptor antagonist
6978166	Naïve	Cinanserin	Systemic (i.v.)	Halothane	Eph	Expressed	Not expressed	5-HT <sub>2A</sub> and 5-HT <sub>2C</sub> receptor antagonist
6976820	Naïve	5-hydroxytryptophan + cinanserin	Systemic (i.p.)	N/A	Beh	Expressed	Expressed	Serotonin precursor + 5-HT <sub>2A</sub> and 5-HT <sub>2C</sub> receptor antagonist
6978166	Naïve	5-hydroxytryptophan	Systemic (i.v.)	Halothane	Eph	Expressed	Expressed	Serotonin precursor
6976820	Naïve	5-hydroxytryptophan	Systemic (i.p.)	N/A	Beh	Expressed	Expressed	Serotonin precursor
27891703	SNL	Citalopram	Systemic (s.c.)	Isoflurane	Eph	Not expressed	Not expressed	SSRI
27891703	SNL	Fluoxetine	Systemic (s.c.)	Isoflurane	Eph	Not expressed	Not expressed	SSRI
32315711	OA MIA (late stage)	Duloxetine	Systemic (s.c.)	N/A	Beh	Not expressed	Expressed	SNRI
32315711	PSNL	Duloxetine	Systemic (s.c.)	N/A	Beh	Not expressed	Expressed	SNRI
32745472	TBI	Duloxetine hydrochloride	Systemic (s.c.)	N/A	Beh	Not expressed	Expressed	SNRI
32745472	TBI	Reboxetine mesylate	Systemic (i.p.)	N/A	Beh	Not expressed	Not expressed	NRI
32745472	TBI	5,7-dihydroxytryptamine + Desipramine hydrochloride	Intrathecal (i.t.) + Systemic (i.p.)	N/A	Beh	Not expressed	Not expressed	Neurotoxin depleting serotonergic fibers + TCA
32745472	TBI	Escitalopram hydrochloride	Systemic (s.c.)	N/A	Beh	Not expressed	Expressed	SSRI
32745472	TBI	Escitalopram + Atipamezole	Systemic (i.p.) + Systemic (s.c.)	N/A	Beh	Not expressed	Expressed	SSRI + $\alpha_2$ -adrenoceptor antagonist
32745472	TBI	5,7-dihydroxytryptamine + Desipramine hydrochloride + Escitalopram	Systemic (i.t.) + Systemic (i.p.) + Systemic (s.c.)	N/A	Beh	Not expressed	Not expressed	Neurotoxin depleting serotonergic fibers + TCA + SSRI
30286616	Naïve	Sumatriptan succinate	Subcutaneous osmotic minipumps	N/A	Beh	Expressed	Not expressed	5-HT <sub>1<math>\alpha</math></sub> receptor agonist
32315711	PSNL	Celecoxib	Orally administered (p.o.)	N/A	Beh	Not expressed	Not expressed	COX-2 inhibitor
32315711	OA MIA (late stage)	Celecoxib	Orally administered (p.o.)	N/A	Beh	Not expressed	Not expressed	COX-2 inhibitor
12818952	Naïve	Isoflurane	Gaseous (inhaled)	Isoflurane	Eph	Expressed	Not expressed for isoflurane above 1.2 MAC	General anaesthetic

**Abbreviations:** SNL - spinal nerve ligation model; TBI - traumatic brain injury; OA MIA - monoiodoacetate model of osteoarthritis; PSLN - partial sciatic nerve ligation; BLS - bright light stress; PAG - periaqueductal grey; i.p. - intraperitoneal, i.th. - intrathecal (L4/L5 - lumbar 4/5); Beh - behaviour, Eph - *in vivo* electrophysiology; EMG - electromyography; IHC - immunohistochemistry; MAC - minimum alveolar anesthetic concentration; TCA - tricyclic antidepressant; SSRI - selective serotonin reuptake inhibitor; NRI - selective noradrenaline reuptake inhibitor; SNRI - selective serotonin-noradrenaline reuptake inhibitor; MOR -  $\mu$ -opioid receptor; KOR -  $\kappa$ -opioid receptor; DOR -  $\delta$ -opioid receptor; COX-2 - cyclooxygenase 2.