



References on the Administration of Enkephalins Using ALZET® Osmotic Pumps

Q3258: A. Normandin, *et al.* Spinal mu and delta Opioids Inhibit Both Thermal and Mechanical Pain in Rats. *Journal of Neuroscience* 2013;33(28):11703-11714

ALZET Comments: [D-Ala2, N-Me-Phe4, Gly5-ol]-enkephalin; CSF/CNS (intrathecal); Rat; mice; animal info (rat - male, adult, Sprague Dawley, 250-300g; good methods (intrathecal catheter placement pg.11704); mice - male, adult, C57BL/6, 20-25g); No pump used, catheter only for lumbar catheterization.

P7610: P. Feng, *et al.* Effects of mu, kappa or delta opioids administered by pellet or pump on oral Salmonella infection and gastrointestinal transit. *European Journal of Pharmacology* 2006;534(1-3):250-257

ALZET Comments: Morphine sulfate; enkephalin analog DPDPE; U50,488H; deltorphin II, D-ala2-; Saline, pyrogen free; SC; Mice; 1003D; 48 hours; Controls received mp w/ vehicle; dose-response (fig 1); comparison of pellets vs. mp; immunology; animal info (female, 6 wk old); mp primed 4 hours in 37 C saline; "morphine pellet potently exacerbated oral salmonella infection, but morphine given by pump, at doses which were immunosuppressive had a substantially lesser effect (of infection)." (p. 251). "Further, we and others have found that morphine pellets induce sepsis in mice." (p. 251).

P6537: P. J. McLaughlin, *et al.* Opioid growth factor inhibition of a human squamous cell carcinoma of the head and neck in nude mice: Dependency on the route of administration. *INTERNATIONAL JOURNAL OF ONCOLOGY* 2004;24(1):227-232

ALZET Comments: Enkephalin; Saline; SC; Mice (nude); 2004; 28 days; Controls received mp w/ vehicle; OGF plasma levels taken; comparison of IP and intratumoral injections vs. SC mp; adverse reaction: (see pg. 229) "within 2 days...3 minipumps containing saline were spontaneously dislodged." [possible pocket too small]; cancer (carcinoma); peptides; enkephalin was met⁻⁵ and termed OGF or opioid growth factor.

P5865: S. Vonhof, *et al.* Tolerance and dependence following chronic intracerebroventricular infusions of Tyr-D-Arg(2)-Phe-Sar(4) (TAPS). *European Journal of Pharmacology* 2003;459(1):41-48

ALZET Comments: Morphine sulfate; Enkephalin analog DAMGO; Dermorphin-derived tetrapeptide (TAPS); CSF, artificial; CSF/CNS; Rat; 2001; 6 days; Controls received mp w/ vehicle; comparison of bolus injections vs. chronic mp; pumps replaced on day 4 to achieve 6 days due to dead space in catheter; ALZET brain infusion kit used; tolerance; dependence; peptides; second hole with guide cannula & stylet used for bolus injections; (ALZET) cannula placement confirmed by fast green dye & the guide cannula confirmed by methylene blue; TAPS is a potent mu-opioid receptor agonist.

P6116: K. Kuzume, *et al.* Sustained exogenous administration of Met(5)-enkephalin protects against infarction in vivo. *American Journal of Physiology-Heart and Circulatory Physiology* 2003;285(6):H2463-H2470

ALZET Comments: Enkephalin; Saline; SC; Rabbit; 2ML1; 24 hours; Controls received mp w/ vehicle; cardiovascular; peptides; enkephalin was met⁻⁵.

P4965: Z. Vertes, *et al.* Epidermal growth factor influenced by opioid peptides in immature rat uterus. *Journal of Endocrinological Investigation* 2000;23(502-508)

ALZET Comments: Enkephalin analog; Naloxone; Saline; IP; Rat; 1003D; 1-3 days; controls received mp w/ vehicle; functionality of mp verified by aspirating remaining contents; peptides; Enkephalin analog ENK was (D-Met2-Pro5)enkephalinamide, inhibits epidermal growth factor.

P3465: I. H. Jonsdottir, *et al.* Chronic intracerebroventricular administration of b-endorphin augments natural killer cell cytotoxicity in rats. *Regul. Pept* 1996;62(113-118)

ALZET Comments: Endorphin, B-; Enkephalin, leucine-; Enkephalin, methionine-; Dynorphin A; SC; CSF/CNS; Rat; 2001; 2ML1; 6 days; controls received saline infusion; peptides; ALZET brain infusion kit used.

P3476: D. P. Menard, *et al.* Alteration of calcitonin gene related peptide and its receptor binding sites during the development of tolerance to mu and delta opioids. *Can. J. Physiol. Pharmacol* 1995;73(1089-1095)

ALZET Comments: Morphine sulfate; Naltrexone; Enkephalin; U-50,488H; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; tolerance.



P2919: T. Rubino, *et al.* Effect of chronic exposure to naltrexone and opioid selective agonists on G protein mRNA levels in the rat nervous system. *Mol. Brain Research* 1994;23(333-337)

ALZET Comments: Naltrexone; DAGO; Enkephalin analog DADLE; DPDPE; U-50,488H; SC; CSF/CNS; Rat; 2001; 7 days; DAGO is a mu-opioid agonist; DPDPE is a delta-opioid agonist.

P2513: R. U. Chukwuocha, *et al.* The in vivo effects of opioid peptides on the murine immune response. *Int. J. Immunopharmac* 1994;16(3):205-215

ALZET Comments: Enkephalin; PBS; mice; 1003D; no duration posted; no stress (see pg. 207); immunology; agents are met-enkephalin, DTLET, FK 33-824; pump implantation has no significant effect on humoral immune response as compared with sham-op and untreated animals (p. 208).

P3137: Y. Takano, *et al.* Chronic spinal infusion of dexmedetomidine, ST-91 and clonidine: spinal alpha2 adrenoceptor subtypes and intrinsic activity. *J. Pharmacol. Exp. Ther* 1993;264(1):327-335

ALZET Comments: Dexmedetomidine; Clonidine; Enkephalin analog ST-91; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; controls received mp with vehicle; tolerance; externalized loop of tubing allowed cessation of flow; dose-response (pg. 330); antihypertensive.

P2630: C. W. Stevens, *et al.* Studies of morphine and D-ala2-D-leu5-enkephalin (DADLE) cross-tolerance after continuous intrathecal infusion in the rat. *Anesthesiology* 1992;76(4):596-603

ALZET Comments: Morphine sulfate; Enkephalin analog DADLE; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; controls received mp w/ vehicle; dose-response (pg.600); stability of morphine in spinal cord assessed; tolerance; "cont. spinal infusion, in contrast to . . . avoids the peak and trough or exponentially decreasing concentration of tolerogen and the receptor during exposure period"; y-catheter used for intrathecal infusion.

R0132: T. L. Yaksh. Tolerance: factors involved in changes in the dose-effect relationship with chronic drug exposure. In 'Towards a new pharmacotherapy of pain', A. I. Basbaum & J. -M. Besson (eds), John Wiley & Sons Ltd 1991;

ALZET Comments: Morphine; Sufentanil; Enkephalin; Saline; IV; CSF/CNS (intrathecal); CSF/CNS; Rat; 7 days; controls received mp w/vehicle; dose-response (p. 163); tolerance; pain; reference of mp pump study on pp. 162-164.

P1273: C. W. Stevens, *et al.* Time course characteristics of tolerance development to continuously infused antinociceptive agents in rats spinal cord. *J. Pharmacol. Exp. Ther* 1989;251(1):216-223

ALZET Comments: Enkephalin analog ST-91; Enkephalin analog DADLE; Enkephalin analog DAMGO; Morphine; Sufentanil; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; no comment posted.

P1612: C. W. Stevens, *et al.* Magnitude of opioid dependence after continuous intrathecal infusion of mu and delta-selective opioids in the rat. *Eur. J. Pharmacol* 1989;166(467-472)

ALZET Comments: Sufentanil citrate; Enkephalin analog DADLE; Enkephalin analog DAMGO; Morphine; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; tissue infusion; dose-response; peptides; tolerance, dependence.

P1560: C. Stevens, *et al.* Potency of infused spinal antinociceptive agents is inversely related to magnitude of tolerance after continuous infusion. *J. Pharmacol. Exp. Ther* 1989;250(1):1-8

ALZET Comments: Enkephalin analog DADLE; Enkephalin analog DAMGO; Enkephalin analog ST-91; Morphine sulfate; Sufentanil citrate; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; mp connected to Y-catheter; dose-response; peptides.

P1562: R. D. Russell, *et al.* Alternative delta and mu receptor activation: a strategem for limiting opioid tolerance. *Pain* 1989;36(381-389)

ALZET Comments: Enkephalin analog DADLE; Saline; CSF/CNS (intrathecal); Rat; 2001; 6, 12 days; pump replaced weekly; neuroscience.

P1183: C. W. Stevens, *et al.* Spinal infusion of opiate and alpha-2 agonists in rats: tolerance and cross-tolerance studies. *J. Pharmacol. Exp. Ther* 1988;244(1):63-70



ALZET Comments: Enkephalin analog ST-91; Morphine sulfate; Saline; CSF/CNS (intrathecal); Rat; 2001; 1 week; controls received mp w/ saline; mp connected to 'Y' catheter; 3 doses of agent infused; concomitant infusion of agents.

P0980: R. D. Russell, *et al.* Continuous intrathecal opioid analgesia: Tolerance and cross-tolerance of mu and delta spinal opioid receptors. *J. Pharmacol. Exp. Ther* 1987;240(1):150-158

ALZET Comments: Enkephalin agonist DADLE; PL 017; Saline; CSF/CNS (intrathecal); Rat; 5 days; controls received mp w/saline; mp connected to intrathecal catheter; peptides.

P0812: T. Shimazu, *et al.* Chronic infusion of norepinephrine into the ventromedial hypothalamus induces obesity in rats. *Brain Research* 1986;369(1/2):215-223

ALZET Comments: Acetylcholine chloride; Cefalotin; Cholecystokinin tetrapeptide; Epinephrine HCl; Bombesin; Endorphin, B-; Enkephalin, methionine-; Norepinephrine HCl; Saline; Sodium bisulfite; CSF/CNS (hypothalamus); Rat; 2002; 5-20 weeks; Cholinergic agent; pumps replaced periodically; mp connected to perm. steel cannula in hypothalamus; cannula fitted w/removable protector; (see p.217); agents infused sep. (cefalotin infused w/each agent); long-term study; peptides.

P0617: R. Vinayek, *et al.* Tolerance and cross-tolerance to the antisecretory effects of enkephalins on the guinea-pig ileal mucosa. *J. Pharmacol. Exp. Ther* 1985;232(3):781-785

ALZET Comments: Enkephalin agonist DADL; Fentanyl citrate; Saline; SC; Guinea pig; 2001; 5 days; comparison of agents effects; controls were sham-operated only; peptides.

P0482: R. Schulz, *et al.* Receptor preference of dynorphin A fragments in the mouse vas deferens determined by different techniques. *J. Pharmacol. Exp. Ther* 1984;230(1):200-204

ALZET Comments: Dynorphin A(1-8); Bestatin; Captopril; Dynorphin A; Enkephalin agonist DADL; Fentanyl; Thiorphan; Saline; SC; vas deferens; Mice; 2001; 2ML1; no duration posted; Comparison of agents effects; 2ML1 pump used w/ captopril, thiorphan, and bestatin; DADL & FEN admin. sc; peptides; antihypertensive.

P0509: L. C. Saland, *et al.* Chronic infusion of opiate peptides to rat cerebrospinal fluid with osmotic minipumps. *Anat. Rec* 1984;210(115-123)

ALZET Comments: Endorphin, a-; Endorphin, ovine B-; Enkephalin, methionine-; Naloxone HCl; Saline; CSF/CNS; Rat; 2001; 1-2 days; comparison of agents effects; peptides.

P8160: D. S. Baskin, *et al.* Dynorphin (1-13) improves survival in cats with focal cerebral ischaemia. *Nature* 1984;312(5994):551-552

ALZET Comments: Enkephalin, Leu-; dynorphin; dynorphin (3-13); Saline; SC; Cat; 2ML1; 7 days; Controls received mp w/ vehicle; peptides; post op. care (penicillin E, lactated ringer's solution); ischemia (cerebral); animal info (adult, male, MCAO).

P0252: M. Wuster, *et al.* The development of opiate tolerance may dissociate from dependence. *Life Sci* 1982;31(1695-1698)

ALZET Comments: Enkephalin agonist DADL; Morphine; SC; Guinea pig; no duration posted; Confusing paper; refers to previous mp papers in methods & mtls. so mp used but not actually mentioned; not sure of agents used; peptides.

P0240: L.-F. Tseng. Tolerance and cross tolerance to morphine after chronic spinal D-Ala2-D-Leu5-enkephalin infusion. *Life Sci* 1982;31(987-992)

ALZET Comments: Enkephalin agonist DADL; Naloxone; Saline; CSF/CNS (intrathecal); Rat; 2001; 5 days; agents infused alone and/or concomitantly; peptides.

P0281: P. Rubini, *et al.* Opiate receptor binding studies in the mouse vas deferens exhibiting tolerance without dependence. *Arch. Pharmacol* 1982;319(142-146)

ALZET Comments: Enkephalin agonist DADL; SC; Guinea pig; mice; 2001; 2ML1; 1 week; 2001 (mice), 2ML1 (GP); peptides.

P0096: E. T. Wei. Enkephalin analogs and physical dependence. *J. Pharmacol. Exp. Ther* 1981;216(1):12-18



ALZET Comments: Enkephalin analog; Morphine sulfate; Water; CSF/CNS (caudal aquaduct); Rat; 1701; 3 days; 1701 (also pump that delivers 1.4 ul/hr.??), 3 days; if pump malfunctioned (catheter dislodged, etc), same pump reimplanted into another animal; peptides.

P0170: R. Schulz, *et al.* Functional opiate receptors in the guinea-pig ileum: their differentiation by means of selective tolerance development. *J. Pharmacol. Exp. Ther* 1981;219(2):547-550

ALZET Comments: DsThr; Enkephalin agonist DADL; Fentanyl; FK-33824; MR-2034; MRZ; Normorphine; Water; SC; Guinea pig; 2001; 6 days; peptides.

P0127: R. Schulz, *et al.* Differentiation of opiate receptors in the brain by the selective development of tolerance. *Pharmacol. Biochem. Behav* 1981;14(75-79)

ALZET Comments: Enkephalin analog DADLE; Sufentanil; CSF/CNS; SC; Rat; 2001; 7-8 days; comparison of chronic vs. acute infusion of DADL; DADL infused ivt, SUF infused sc; peptides.

P0173: R. Schulz, *et al.* Are there subtypes (isoreceptors) of multiple opiate receptors in the mouse vas deferens. *Eur. J. Pharmacol* 1981;76(61-66)

ALZET Comments: Endorphin, a-neo-; DsThr; Dynorphin; Enkephalin analog DADLE; FK-33824; MR-2034; MRZ; Normorphine; Sufentanil; Water; SC; mice; 2001; 6 days; peptides; MRZ is 5,9-dimethyl,2'S-5,9-dimethyl-2'-hydroxy-2-(2-methoxy-propyl)-6,7-benzomorphan, a kappa opioid agonist.

P0119: M. Wuster, *et al.* The direction of opioid agonists towards μ -, κ - and ϵ -receptors in the vas deferens of the mouse and rat. *Life Sci* 1980;27(163-170)

ALZET Comments: Enkephalin analog DADLE; Sufentanil; SC; mice; 2001; 6 days; peptides.

P0102: M. Wuster, *et al.* Highly specific opiate receptors for dynorphin-(1-13) in the mouse vas deferens. *Eur. J. Pharmacol* 1980;62(2/3):235-236

ALZET Comments: Enkephalin analog DADLE; Sufentanil; SC; mice; 2001; 6 days; simultaneous infusion of agents; peptides.

R0046: P. Skett, *et al.* The effect of pituitary hormones on hepatic drug metabolism. In 'Biochemistry, Biophysics and Regulation of Cytochrome P-450,' J. -A. Gustafsson, J. Carlstedt-Duke, A. Mode, and J. Rafter (eds.), Elsevier/North-Holland, Amsterdam 1980;195-198

ALZET Comments: Enkephalin analog DADLE; Follicle stimulating hormone; Growth hormone, bovine; Growth hormone, rat; Pituitary extract; Prolactin, bovine; Prolactin, rat; Thyroid-stimulating hormone; Water; SC; Rat; 1701; 1 week; peptides.

P0113: R. Schulz, *et al.* Lack of cross-tolerance on multiple opiate receptors in the mouse vas deferens. *Mol. Pharmacol* 1980;18(3):395-401

ALZET Comments: Enkephalin analog DADLE; Etorphine; Sufentanil; SC; mice; 2001; 1, 3, or 6 days; separate & simultaneous infusion of agents; peptides.

P0101: R. Schulz, *et al.* Selective development of tolerance without dependence in multiple opiate receptors of mouse vas deferens. *Nature* 1980;285(5762):242-243

ALZET Comments: Enkephalin analog DADLE; Sufentanil; SC; mice; 1701; 6 days; peptides.

R0015: E. Wei. Enkephalin analogs and physical dependence. Presented at the International Narcotics Research Conference, June 9-13, Falmouth, MA 1979;

ALZET Comments: Enkephalin analog; no duration posted; no comment posted.

P0030: E. Wei. Enkephalin Analogs: Correlation of potencies for analgesia and physical dependence. In 'Characteristics and Function of Opioids,' J. M. Van Ree and L. Terenius (eds.), Elsevier/N. Holland Biomedical Press, Amsterdam 1978;445-446

ALZET Comments: Enkephalin analog; CSF/CNS (fourth ventricle); Rat; no duration posted; no comment posted.

P0001: E. Wei, *et al.* Physical dependence on opiate-like peptides. *Science* 1976;193(1262-1263)



ALZET Comments: Morphine sulfate; methionine-enkephalin; endorphin, B-; Water; CSF/CNS (frontal cortex); CSF/CNS (periaqueductal gray); Rat; 70 hours; peptides; dependence; 1 ul/hr pumps used.

R0003: E. Wei, *et al.* Chronic, intracerebral infusion of morphine and peptides with osmotic minipumps, and the development of physical dependence. Presented at the International Narcotics Research Conference, July 22, Aberdeen, Scotland 1976;

ALZET Comments: Endorphin, a-; Endorphin, B-; Enkephalin, leucine-; Enkephalin, methionine-; Morphine sulfate; no duration posted; no comment posted.