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Review

Endogenous Opiates and Behavior: 2016

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ABSTRACT

This paper is the thirty-ninth consecutive installment of the annual review of research concerning the endogenous opioid system. It summarizes papers published during 2016 that studied the behavioral effects of molecular, pharmacological and genetic manipulation of opioid peptides, opioid receptors, opioid agonists and opioid antagonists. The particular topics that continue to be covered include the molecular-biochemical effects and neurochemical localization studies of endogenous opioids and their receptors related to behavior, and the roles of these opioid peptides and receptors in pain and analgesia, stress and social status, tolerance and dependence, learning and memory, eating and drinking, drug abuse and alcohol, sexual activity and hormones, pregnancy, development and endocrinology, mental illness and mood, seizures and neurologic disorders, electrical-related activity and neurophysiology, general activity and locomotion, gastrointestinal, renal and hepatic functions, cardiovascular responses, respiration and thermoregulation, and immunological responses.

1. Introduction

This thirty-ninth installment of the annual review of research concerning the endogenous opioid system summarizes published papers during 2016 that studied the behavioral effects of molecular, pharmacological and genetic manipulation of opioid peptides, opioid receptors, opioid agonists and opioid antagonists. This review continues the excellent tradition initiated by Drs. Abba Kastin, Gayle Olson, Richard Olson, David Coy and Anthony Vaccarino in the reviews spanning from 1978 through 2000. As begun in the summaries of papers published over the past fifteen years (2001–2015 papers), two major sections of the review have been added because of the rapid and large expansion of the field. The first (Section 2) is the molecular-biochemical effects and neurochemical localization studies of endogenous opioids and their receptors especially as they may eventually relate to behavior. The second is the examination of the roles of these opioid peptides and receptors in their most studied aspect, pain and analgesia in animals (Section 3) and humans (Section 4) as well as examining opioid and nonopioid mediation of other analgesic responses (Section 5). As with the previous reviews, subsequent sections will cover the roles of opioid peptides and receptors in the areas of stress and social status (Section 6); tolerance and dependence (Section 7); learning and memory (Section 8); eating and drinking (Section 9); drug abuse and alcohol (Section 10); sexual activity and hormones, pregnancy, development and

Abbreviations: Ach, acetylcholine; ADHD, attention-deficit hyperactivity disorder; BDNF, brain-derived neurotrophic factor; BEND, beta-endorphin; BFNA, beta-funaltrexamine; Ca(2+), calcium; CAMK, calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; CB, cannabinoid; CCK, cholecystokinin; CFA, complete Freund's adjuvant; COMT, catechol-O-methytransferase; COPD, chronic obstructive pulmonary disease; C/P, caudate/putamen; CREB, Ca(2+)/cAMP responsive element binding protein; CRF, corticotropin factor; DA, dopamine; DADL, D-Ala(2), D-Leu(5)-enkephalin; DALDA, D-Arg-Phe-Lys-NH2; DAMGO, D-Ala(2), Nme(4), Gly-ol(5)-enkephalin; Delt, deltorphin; DPDPE, D-Pen(2), D-Pen(5)-enkephalin; DREAM, downstream regulatory element antagonistic modulator; DRN, dorsal raphe nucleus; DRG, dorsal root ganglion; DYN, Dynorphin; EEG, encephalographic; Enk, enkephalin; EPSP, excitatory post-synaptic potential; ERK, extracellular regulated signal kinases; FSH, follicle stimulating hormone; GI, gastrointestinal; GIRK, G-protein inwardly rectifying K+ channel subunit; GnRH, gonadotropin-releasing hormone; GPCR, G protein coupled receptor; HIV, human immunodeficiency virus; HPLC, high-performance liquid chromatography; HR, heart rate; ICSS, intracranial self-stimulation; ICU, intensive care unit; K(+), potassium; KO, knockout; KNDy, kisspeptin-neurokinin B-dynorphin; LC, locus coeruleus; LC–MS, liquid chromatography–mass spectrometry; Lenk, leu-enkephalin; LH, leutinizing hormone; L-DOPA, l-dihydroxyphenylalanine; L-NAME, N(omega)-nitro-l-arginine methyl ester; LPS, lipopolysaccharide; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; MAP, mean arterial pressure; MAPK, mitogen-activated protein kinase; MCH, melanin concentrating hormone; MDMA, 3,4-methylenedioxy-methamphetamine; Menk, met-enkephalin; 6MAM, 6-monoacetylmorphine; mPFC, medial prefrontal cortex; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRI, magnetic resonance imaging; NAC, nucleus accumbens; NBNI, nor-binaltorphamine; NE, norepinephrine; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NOP, orphan-like opioid receptor; NPY, neuropeptide Y; NSAID, non-steroidal anti-inflammatory drug; NRM, mucleus raphe magnus; NTI, naltrindole; NTS, nucleus tractus solitarius; OPRM1, mu opioid receptor gene; OFQ/N, nociceptin; 6-OHDA, 6-hydroxydopamine; PAG, periaqueductal gray; PCA, patient-controlled analgesia; PDYN, pro-dynorphin; Penk, pro-enkephalin; PET, positron emission tomography; PKA, protein kinase A; PKC, protein kinase C; POFQ/N, pro-orphain FQ/nociceptin; POMC, pro-opiomelanocortin; PPAR, peroxisome proliferator-activated receptor; PTSD, post-traumatic stress disorder; PVN, paraventricular nucleus; RNA, ribonucleic acid; RVM, rostral ventromedial medulla; 5-HT, serotonin; SN, substantia nigra; SNP, single nucleotide polymorphism; SON, supraoptic nucleus; SP, substance P; STZ, streptozotocin; TENS, transcutaneous electrical nerve stimulation; TH, tyrosine hydroxylase; THC, tetrahydrocannibinol; TMJ, temporomandibular joint; TNF, tumor necrosis factor; TP, testosterone proprionate; TRPV1, transient receptor potential vanilloid subfamily member 1; VP, vasopressin; VTA, ventral tegmental area

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endocrinology (Section 11); mental illness and mood (Section 12); seizures and neurologic disorders (Section 13); electrical-related activity and neurophysiology (Section 14); general activity and locomotion (Section 15); gastrointestinal, renal and hepatic functions (Section 16); cardiovascular responses (Section 17); respiration and thermoregulation (Section 18); and immunological responses (Section 19). To accommodate these additional large sections, only published articles are covered in this review; published abstracts from scientific meetings are not covered, but will be added as they are published in the scientific literature. Although this review is largely an anthology of the previous year's publications, particular topics in the current review begin with a section labeled “Highlights”. These are articles that in the opinion of the author accomplished one of two criteria. The first type of articles provided new and novel research findings, insights or techniques that advanced the field for future work. The second type of articles built on already-existing knowledge, but the breadth and scope of the findings deserved attention. It should be noted that such “Highlights” are subjective on the part of the author. Finally, some articles published in 2015 that were not included in the previous review are found here. Given the scope of this review, a paper may be inadvertently overlooked. If this is the case, please accept my apologies, and send the citation and abstract to richard.bodnar@qc.cuny.edu, and I will include it in the next yearly review.

2. Endogenous opioids and receptors

2.1. Molecular-biochemical effects of mu agonists and receptors

Highlights: Consituttive desensitization of mu and delta opioid receptors in peripheral sensory neurons was mediated by beta-arrestin-2 [976]. Mu opioid receptor expression after morphine administration was regulated by the miR-212/132 cluster [304]. Heterogeneity was confirmed for intracellular loop 3 of the mu opioid receptor GPCR [418]. Morphine-, DAMGO- and fentanyl-induced stimulation at human mu opioid receptors in a [(35)S]GTPgammaS incorporation assay revealed a “bell-shaped” concentration-response relationship under conditions of strong G protein coupling [395]. Gi/o proteins and phospholipase C-delta1 were critical in the activation of mu opioid receptor-operated TRPC-4 channels [1002]. NF1 deletion prevented opioid activation of Ras in the striatum [1129]. Morphine caused a G-beta-epsilon-dependent increase in plasma membrane PKC in kidney HEK 293 cells overexpressingmu opioid receptors [364]. Biased mu opioid receptor agonists (DAMGO, endomorphin-2) diversely regulate lateral mobility in the plasma membrane and functional coupling of the receptor to its cognate G proteins [706]. Methadone was characterized as a beta-arrestin-biased mu opioid receptor agonist [222]. Cytochrome P450 3A enzymes catalyzed the O6-demethylation of thebaine, a key step in endogenous mammalian morphine biosynthesis [547].

Morphine-induced mu opioid receptor-1X and ASF/SF2 expressions acted independent of transcriptional regulation [856]. Biased mu opioid receptor agonists retained their uniqueness across different cell backgrounds [1006]. Simultaneous determination of codeine, codeine-6-glucuronide, norcodeine, morphine, M3G and M6G could be performed in post-mortem blood, vitreous fluid, muscle, fat and brain tissue by LC–MS [294]. Morphine up-regulated surface 5-HT3A receptors [740]. Electromagnetic field stimulation inhibited cAMP more than morphine in a human mu opioid receptor cell model [884]. Pharmacoepigenetics revealed a minor role for DNA methylation in mu opioid receptor expression in different human brain regions [527]. The rank-order of mu opioid receptor agonists using Na(+),K(+)-ATPase as an effector mechanism was morphine > levorphanol > buprenorphine > fentanyl [691]. Lipid composition increased receptor conformation on the spatio-temporal organization of mu opioid receptors in a multi-component plasma membrane model [681]. Morphine respectively decreased and increased ERK1/2 phosphorylation in the NAC of rats and mice [878]. Morphine glucuronidation and elimination were decreased in intensive care patients relative to healthy volunteers [13]. Morphine inhibits the soluble guanylate cyclase-NO pathway according to a mathematical model [90]. Morphine stimulated NO release in human mitochondria [968]. Neither morphine nor quinidine, a strong P-glycoprotein inhibitor, affected the pharmacokinetics and central nervous system distribution of naloxogel [123]. Possible binding sites for morphine and nicardipine were identified on the multidrug transporter P-glycoprotein using umbrella sampling techniques [974]. A next-generation sequencing of human opioid receptor genes was accomplished based on a custom AmpliSeq library and ion torrent personal genome machine [550]. The mu opioid receptor was further evaluated using novel antagonists and structural modeling [488]. A morphine like substance and mu opioid receptor expression were observed in a canine parasite, Toxacara canis (Nematoda: Ascaridae) [337].

Serum and urine concentrations of morphine and the morphine metabolites, M6G and M3G were highly correlated in patients with advanced cancer receiving continuous intravenous morphine [591]. Disposition of morphine, M3G and M6G in plasma was best described by a one-compartment model in young children after a single oral dose [1048]. A HPLC-tandem mass spectrometric method was developed for simultaneous quantification of morphine, M3G, M6G, hydromorphone and normorphine in serum [909]. Quantification of morphine, M6G, bupremorphine and the enantiomers of methadone could be achieved by enantioselective mass spectrometric chromatography in whole blood [173].

The dynamic assembly and disassembly of functional BEND amyloid fibrils were described [763]. Ultraviolet B stimulated POMC signaling in the arcuate nucleus of the hypothalamus in mice [954]. A novel non-opioid binding site for endomorphin-1.was identified that is not coupled to G-proteins [594]. Novel endomorphin analogues containing alpha-hydroxy-beta-phenylalanine (AHPBA) displayed mixed MOR/DOR agonist and DOR antagonist activities [411]. Human dipeptidyl peptidase III linked to endomorphin-2, Menk and Lenk revealed mechanisms of enzyme inhibition [558].

DAMGO, but not fentanyl in the ventrolateral PAG induced ERK1/2 phosphylation which was blocked by inhibitn receptor internalization [102]. A high throughput screening procedure was employed to identify new biased mu opioid receptor agonists relative to DAMGO [1121]. Increased brain delivery of the opioid peptide DAMGO was elicited by gluthione-PEGlycated liposomes [633]. The efflux transporters Pgp and Bcrp were not responsible for DAMGO efflux [632]. [Dmt(1)]DALDA analogues modified with tyrosine analogues at position 1 displayed mu opioid receptor affinity [126]. Dimeric dermorphin analogs modified with beta3-homo-amino acids displayed strong mu opioid receptor affinity [288].

CYP2D6 phenotype-specific codeine population pharmacokinetics revealed differential conversion to morphine and M6G [630]. Population pharmacokinetics of nalmefene in healthy subjects revealed 24 h of therapeutic mu opioid receptor occupancy [567]. Oxycodone and morphine analytes could be detected in urine to test adherence [577]. Mu, delta and kappa opioid receptor binding were observed for indium (III) and [111In]-labeled macrocyclic conjugates of diprenorphine to identify novel ligands desgined for imaging studies of peripheral opioid receptors [965]. Novel peripheral morphiceptin analogs were synthesized and acted at mu and kappa opioid receptors [11]. Morphinan alkaloids were synthesized in Saccharomyces cerevisiae [287].

The pharmacokinetics of multiple-dose buprenorphine buccal film reached steady stat e within 3 days in healthy volunteers [67]. Methadone and BMS986122 dispalyed differential agonist binding characteristics at the human mu opioid receptor [79]. A blocking group scan using a spherical organometallic complex identified an unprecedented mu opioid receptor binding mode with potent activity in vitro and in vivo for the opioid peptide dermorphin [973]. Beta-azido(or 1-piperidinyl)methylamino acids in position 2 or 3 produced differential confirmation on dermorphin analogues [662]. A cyclic tretrapeptide (“Cyclodal”) and its mirror-image isomer were both identified as high-affinity mu opioid receptor antagonists [1108]. Ignavine was a positive