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Review

Contributions of peripheral, spinal, and supraspinal actions to analgesia

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ABSTRACT

Pain signaling involves several main compartments that can be considered as potential sites for analgesic drug actions. When drugs are given systemically, they can act at spinal, supraspinal and peripheral sites, and several methods have been developed for identifying where they act. These include (1) localized delivery of drugs to specific sites (via intracerebral, intrathecal, and intraplantar injections), (2) systemic delivery of drugs with localized delivery of antagonists for the receptor on which the drug acts or for a system recruited by the drug, (3) use of peripherally restricted analogs, and (4) use of conditional knockout technology to selectively deplete receptors on nociceptors. Delivery of drugs simultaneously to several sites (spinal/supraspinal, peripheral/spinal, and peripheral/supraspinal) reveals "self-synergy" between sites for some agents. Knowledge of peripheral contributions to drug actions is important because of the potential to develop peripherally restricted analgesics (with a diminished side effect profile due to not entering the central nervous system), the potential to deliver drugs peripherally (e.g. topically) to act on sensory nerve endings and adjacent tissue (with a diminished side effect profile due to limited systemic absorption), and the potential to use combinations of topical and oral drug regimens to obtain improved pain relief (without increasing the side effect burden). This review considers methods used for compartmental analysis, and results of such site analysis for several major classes of analgesic drugs that are in current use.

Contents

Abbreviations: CB, cannabinoid; CNS, central nervous system; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; GABA, γ-aminobutyric acid; 5-HT, serotonin; i.c.v., intracerebroventricular; i.pl., intraplantar; i.t., intrathecal; i.v., intravenous; NA, noradrenaline; NLXM, naloxone methiodide; NMDA, *N*-methyl-D-aspartate; NSAID, non-steroidal anti-inflammatory drug; SNRI, selective noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TRP, transient receptor potential; WIN, WIN 55,212-2

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1. Introduction

Pain signaling has several main components, including sensory afferent input to the spinal cord, transmission to supraspinal sites, supraspinal integration, and descending regulation; modulation of pain can occur within each of these domains. Specific pain states can involve increases in signaling in these components, and several reviews over the past few years have elaborated molecular, cellular and network processes involved (Basbaum et al., 2009; Latremoliere and Woolf, 2009; Gold and Gebhart, 2010; Ossipov et al., 2010). Inflammation and neuropathic pain represent major pain categories and involve increased afferent signaling (peripheral sensitization), increased pain transmission (spinal sensitization), and altered central pain connectivity (integration and modulation). Most analgesic drugs (opioids, non-steroidal anti-inflammatory drugs or NSAIDs, antidepressants, anticonvulsants, and other adjuvants) are given systemically, and each agent has the potential to act at peripheral, spinal and supraspinal sites. The relative contribution of these sites to the analgesic action of each drug often is not clear, but with several approaches now available to address this issue, compartmental analysis of drug actions is receiving more attention. There are several reasons why knowing the contributions of compartments to efficacy is important. Some systemic analgesics have an adverse effect profile that is due to actions within the central nervous system (CNS); if there is a prominent peripheral component to analgesia, development of peripherally restricted agents that do not cross the blood–brain barrier and access central sites may represent a useful therapeutic strategy to minimize adverse effects. In addition, peripheral delivery of drugs (e.g. topical applications of cream, gel, or patch) to target afferent input can lead to low systemic drug levels and fewer adverse effects; this approach holds considerable promise for the development of novel formulations. Spinal sites of drug action also are amenable to localized delivery approaches using epidural and intrathecal (i.t.) administration, but there are risks involved in these forms of delivery and usage is limited to specialized settings. Furthermore, while preclinical studies consistently reveal spinal sites of action for a variety of drugs, there is a need to attend to potential neurotoxicity following spinal drug administration (e.g. Yaksh et al., 2008).

The purpose of this review is to highlight approaches that have been useful for elaborating the involvement of specific compartments in drug actions in preclinical models, and to consider key findings in relation to compartmental actions of drugs within several major analgesic classes. Considerations will focus particularly on the peripheral compartment because there are several potential practical consequences to understanding this contribution. The main focus of the review is conceptual, and it is not intended to be a systematic or comprehensive survey.

2. Methods of investigation

2.1. Selective delivery of analgesics to supraspinal, spinal and peripheral sites

With the development of methods that can deliver drugs supraspinally (via intracerebroventricular, i.c.v., or intracerebral delivery to discrete brain sites; using acute i.c.v. puncture in mice or cannulas implanted into discrete brain regions in rats), spinally (via acute lumbar puncture, or via chronically implanted i.t. cannulas), and peripherally (using intraplantar, i.pl., delivery to the hindpaw, or intra-articular delivery to the knee joint), it has become possible to deliver small quantities of drugs directly to respective compartments and implicate particular sites of action in drug effects (Sections 3–7). Each of these approaches has some limitations. Supraspinal injections may be limited by the accuracy of the injection site when brain regions are small (can be analyzed post-hoc by injection of markers to identify placement sites anatomically), and also by inflammatory or other tissue adaptations to the presence of an implanted cannula (needs to be considered when interpreting results). Spinal injections delivered by chronically implanted i.t. cannulas (Malkmus and Yaksh, 2004) may be limited by inflammatory and tissue reactions (DeLeo et al., 1997), and the potential for such factors to influence results needs to be considered. Peripheral injections may be limited by dosage, as i.pl. administration can simply represent another systemic route of administration; an adequate control for this is to inject into the contralateral hindpaw, and if this is inactive, the drug effect can be regarded as being peripheral. In addition, a calculation of the systemic dosage equivalent can provide a useful frame of reference.

Site analysis using the above methods can reveal drug actions at several sites, and there is the potential for interactions between sites. These can be evaluated using applications to multiple sites, and isobolic analysis to determine whether such sites can interact additively, supra-additively (synergistically), or sub-additively (antagonistically). Several combinations are possible, including spinal/supraspinal, spinal/peripheral, and supraspinal/peripheral delivery. Morphine (Yeung and Rudy, 1980) and acetaminophen (Raffa et al., 2000) have undergone this type of site–site analysis, and supra-additive interactions are referred to as “self-synergy”. There are, however, limited numbers of such site–site analysis studies. Furthermore, the relative contribution of these sites to antinociception in inflammatory and neuropathic pain states, where receptor expression on neuronal populations and other cellular targets may be altered by that particular pain state, has received little attention until recently (Section 3).

2.2. Systemic delivery of agonist with spinal, supraspinal and peripheral antagonists

Targeted drug delivery can reveal agonist drug actions at several sites throughout the neuraxis. However, such delivery does not reveal the relative contribution of each site to systemic drug actions because local administration of drug to a specific site can involve delivery of high local concentrations which exceed the tissue levels that occur with systemic delivery. Systemic administration of an agonist along with localized delivery of a receptor antagonist to discrete sites can address this issue. This methodology can be used in different pain states, can potentially reveal differential contributions of compartments in such states, and is amenable to explorations using receptor agonist/antagonist combinations (e.g., systemic morphine + i.t./i.c.v/i.pl. naloxone; systemic cannabinoid $(CB)_1$ receptor agonist + i.t./i.c.v/i.pl. CB_1 receptor antagonist). This methodology is also suited for explorations using antagonists for different receptors, and this approach reveals aspects of the mechanism of action of the agonist. For example, systemic administration of morphine or antidepressants combined with i.t. delivery of antagonists for noradrenaline (NA) or serotonin (5-HT) receptors reveals the involvement of spinal amine actions for these agents. In some cases (morphine), recruitment involves supraspinal activity and subsequent involvement of descending pathways (Jensen and Yaksh, 1986), while in others (antidepressants), it can reflect inhibition of amine uptake within the spinal cord and a more local effect (Nakajima et al., 2012). In both instances there is a net recruitment of descending pain modulatory pathways. In some cases, the analgesic is not a receptor agonist but interacts with several mechanisms; such drugs include acetaminophen, antidepressants and tramadol. With these agents, localized delivery can be useful for revealing both compartmental and mechanistic aspects of their actions. Several