Rapid communication

Opioid receptors and acetaminophen (paracetamol)

Robert B. Raffa*, Ellen A. Walker, Steven N. Sterious

Department of Pharmaceutical Sciences, Temple University School of Pharmacy, 3307 North Broad Street, Philadelphia, PA 19140, USA

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Abstract

We report that the acetaminophen (paracetamol)-induced spinal (intrathecal, i.t.)/supraspinal (intracerebroventricular, i.c.v.) site/site antinociceptive ‘self-synergy’ in mice is attenuated by the opioid receptor subtype selective antagonists β-funaltrexamine hydrochloride (β-FNA; μ), naltrindole (β), and nor-binaltorphine hydrochloride (nor-BNI; κ). These findings further implicate endogenous opioids (viz., endorphins, enkephalins, and dynorphins) and their pathways as contributors to the central antinociceptive action of acetaminophen.

Keywords: Acetaminophen; Paracetamol; Opioid receptor

More than 100 years after its synthesis, the mechanism of analgesic action of acetaminophen (paracetamol; N-acetyl-p-aminophenol) remains unknown. Postulated mechanisms (reviewed by Walker, 1995 and Björkman, 1995), including inhibition of cyclooxygenase isozymes, have been inadequate (Warner et al., 2004). However, recent work in our laboratory has led to the discovery that the analgesic effect of acetaminophen involves recruitment of endogenous opioid pathways that lead to antinociceptive spinal–supraspinal ‘self-synergy’ (Raffa et al., 2000). We also demonstrated a synergistic enhancement of acetaminophen’s antinociceptive action by spinal administration of phentolamine (Raffa et al., 2001), implicating an interaction between descending endogenous opioid pathways and spinal sites. The present study used opioid receptor subtype-selective antagonists to identify the opioid receptor subtype(s) (μ, δ, or κ) involved in the spinal/supraspinal antinociceptive synergy elicited by acetaminophen. Elucidation of the details of this contribution should enhance the understanding of the mechanism of this major analgesic pathway, with possible benefit to novel drug-design efforts.

The methods were similar to those previously reported (Raffa et al., 2000). Male pathogen-free Swiss-derived albino Crl:CD-1®(ICR)BR mice (18–24 g; Charles River Laboratories) were group-housed under controlled conditions of temperature, humidity and 12-h light/dark cycle. Food and water were available ad libitum. Each mouse was used once and was treated in accordance to the principles expressed in the Declaration of Helsinki. The standard abdominal irritant test described by Collier et al. (1968), with minor modifications, was used. Briefly, acetaminophen (45 mg) or vehicle (5% ethanol–distilled water) was injected into the right lateral cerebral ventricle (5 μl), into the subarachnoid space of the subvertebral space between L5 and L6 (5 μl), or both (22.5 μg each site). The mice were then injected with acetylcholine bromide (5.5 mg/kg., intraperitoneally (i.p.)) and observed for up to 10 min for a single characteristic behavioral response as described by Collier et al. (1968). The absence (inhibition) of this response over 10 min was calculated as % antinociception according to: 100×(nonresponders)/group size. The opioid receptor antagonists naloxone hydrochloride (nonselective, 3.6 μg), naltrindole hydrochloride (δ-selective, 5 μg), and nor-binaltorphine hydrochloride (nor-BNI; κ-selective, 5 μg) were administered intrathecally (i.t.) together with acetaminophen or vehicle. The μ-selective β-funaltrexamine hydrochloride (β-FNA; 10 mg/kg, subcutaneously (s.c.))
naloxone suggested that acetaminophen elicits the activation of one or more endogenous opioid pathways (Raffa et al., 2000). However, acetaminophen does not bind to opioid receptors (Raffa and Codd, 1996) and naloxone does not antagonize acetaminophen’s action at a single site (i.c.v. or i.t.); it only attenuates the site/site synergy (Raffa et al., 2000). The present study extends these findings, implicating each of the opioid receptor subtypes and endogenous pathways (endorphin, enkephalin, and dynorphin) to some degree in the overall synergy, possibly in the order κ > μ = δ. Future work obtaining full dose–response curves and other techniques will discriminate the relative contribution of each pathway.

These findings support and extend our hypothesis that the analgesic action of acetaminophen includes a component of activation of descending opioid pathways and synergistic interaction at the level of the spinal cord. Validation awaits a demonstration of some selective binding or other action at these sites. The importance extends beyond this single drug, arguably the most widely used analgesic in the world, to elucidation of the third major analgesic pathway in humans.

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References


