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Peripheral blockade of topical morphine tolerance by ketamine

Yuri A. Kolesnikov, Gavril W. Pasternak *

Department of Anesthesiology and The Cotzias Laboratory of Neuro-Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA

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Abstract

Repeated topical administration of morphine daily produces tolerance within three days. Ketamine alone has little effect in the radiant heat tailflick assay. However, with administered with morphine, topical ketamine prevented the development of morphine tolerance in a dose-dependent manner. Furthermore, topical ketamine also slowly reversed pre-existing morphine tolerance. These observations imply that topical morphine tolerance is mediated, at least in part, through peripheral *N*-methyl-D-aspartate (NMDA) receptors and raises the possibility of the use of topical NMDA receptor antagonists clinically.

Keywords: Opioid; Peripheral; NMDA receptor

Peripheral sites have been implicated in the development of systemic morphine tolerance (Kolesnikov et al., 1996). Topical morphine given daily produced tolerance within three days, shifting the dose-response curve 9-fold shift to the right (Kolesnikov and Pasternak, 1999). *N*-methyl-D-aspartate (NMDA) receptor antagonists can prevent systemic morphine tolerance (Trujillo and Akil, 1991; Ben-Eliyahu et al., 1992) and when given systemically they also prevented tolerance to topical morphine (Kolesnikov and Pasternak, 1999). Recent evidence supports the presence of NMDA receptors on peripheral cutaneous axons (Carlton et al., 1995; Zhou et al., 1996), leading us to speculate on a possible peripheral activity of NMDA antagonists. Ketamine, a clinically available NMDA receptor antagonist with affinity for the phencyclidine site, can reverse morphine tolerance (Shimoyama et al., 1996). However, its clinical utility is limited by psychomimetic side effects. In the current studies, we have investigated the effect of topically administered ketamine on peripheral morphine analgesia and tolerance.

Drugs were administered topically by immersing the tail (3–3.5 cm) in dimethyl sulfoxide (DMSO) solutions containing either ketamine or morphine alone or both drugs together. Tailflick latencies then were determined on the region of the tail immersed in the drug. To ensure a local effect, we also tested a more proximal segment of tail not exposed to the drug solution. Control studies have documented that under these conditions DMSO alone is inactive in the tailflick assay and that drugs administered in this manner act locally with no appreciable systemic absorption (Kolesnikov and Pasternak, 1999). Analgesia was assessed quantally as doubling or greater of baseline latencies in mice in the radiant heat tailflick assay.

Daily topical morphine (15 mM) led to tolerance with the complete loss analgesia by the third day (Fig. 1A and B). The NMDA receptor antagonist ketamine given systemically prevented the development of tolerance to topical morphine, but intrathecal ketamine was ineffective (data not shown). Topical ketamine co-administered with morphine blocked tolerance as effectively as systemic drug in a dose-dependent manner (Fig. 1; left panel). The lower dose (3.6 mM) delayed the appearance of tolerance, but the higher dose (36 mM) effectively blocked tolerance. Ketamine alone had no appreciable effect in this assay.

Topical ketamine also reversed pre-established tolerance (Fig. 1; right panel). After treating mice with a fixed concentration of topical morphine alone for three days the mice displayed no analgesia. Ketamine added to the treatment regime restored analgesic sensitivity over next three days despite the continued administration of morphine.

The ability of topical ketamine to prevent and/or reverse morphine tolerance implies a peripheral mechanism of action and is similar to earlier experiments with dizocilpine (MK-801) (Kolesnikov and Pasternak, 1999).

* Corresponding author. Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021. Tel.: +1-212-639-7046; Fax: +1-212-794-4332; E-mail: pasterng@mskmail.mskcc.org

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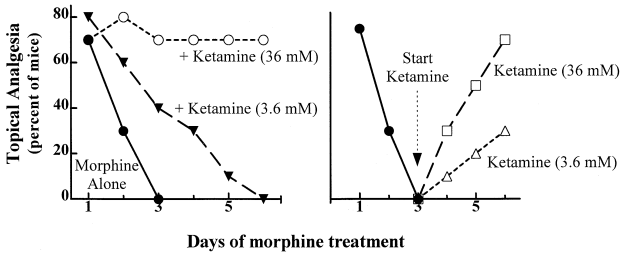

Fig. 1. Effect of ketamine on topical morphine tolerance. Left panel: Groups of mice ($n = 20$) were treated topically once daily for 3 days with morphine (15 mM) alone (closed circles) or both morphine with ketamine at 3.6 mM (triangles) or 36 mM (open circles). Ketamine alone (36 mM) did not produce significant analgesia in this model. After three days, the response to morphine alone was lost ($p < 0.001$). The lower ketamine dose (3.6 mM) significantly lessened the loss of morphine analgesic response after three days ($p < 0.05$). The higher ketamine dose (36 mM) prevented tolerance up to six days ($p < 0.0001$). Right panel: Groups of mice ($n = 20$) received topical morphine (15 mM) alone (closed circles) for two days. Starting on the day 3, the two groups of mice received daily doses of morphine in conjunction with either ketamine at either 3.6 (triangles) or 36 mM (squares) through day 6. The higher ketamine dose (36 mM) completely restored morphine analgesia ($p < 0.0001$).

Mechanistically, these observations are consistent with the possibility that peripheral tolerance is mediated through peripheral NMDA receptors, possibly on the same dorsal root ganglia neurons containing the opioid receptors. Having the NMDA receptor cascade implicated in tolerance located within the same neuron as the opioid receptor being regulated is quite intriguing and deserves further study. Ketamine has much potential clinically based upon its demonstrated utility in animal models. However, its use is hindered by its association with psychotomimetic and dysphoric actions and hallucinations. The ability of using the agent topically and thereby eliminating significant systemic actions may overcome these problems and greatly expand the use of this interesting analgesic adjuvant.

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