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Effects of morphine on the experimental illusion of pain produced by a thermal grill

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Abstract

We compared the effects of systemic morphine on normal (heat and cold) pain and paradoxical burning pain evoked by the simultaneous application of innocuous warm and cold stimuli to the skin. Twelve healthy volunteers participated in a randomised, double-blind, cross-over study to compare the effects of intravenous administration of morphine (0.025 or 0.1 mg/kg) or placebo (saline). Stimuli were applied to the palm of the right hand with a thermode ("thermal grill") composed of six bars, whose temperatures were controlled by Peltier elements. For each session, we measured the heat and cold pain thresholds and then successively measured the intensity of: (i) paradoxical pain evoked by a combination of non-noxious warm and cold stimuli; (ii) "normal" pain evoked by suprathreshold heat or cold stimuli; (iii) non-painful sensations evoked by warm or cold stimuli at temperatures used to produce paradoxical pain. Measurements were performed before 20 min after the administration of morphine or placebo and 5 min after the administration of the morphine antagonist, naloxone. The administration of 0.1 mg/kg of morphine, but not 0.025 mg/kg, induced a significant and naloxone-reversible reduction of paradoxical pain intensity, which was directly correlated with the reduction of normal cold pain. No differences were observed for non-painful thermal sensations. The paradoxical burning pain evoked by a thermal grill can be modified pharmacologically by analgesics and share some mechanisms with normal pain. This unique experimental "illusion of pain" may represent a new model to test analgesics in healthy volunteers.

Keywords: Human pain model; Psychophysic; Allodynia; Thermal sensory system

1. Introduction

The paradoxical burning pain induced by the simultaneous application of innocuous warm and cool stimuli to the skin is a unique experimental phenomenon, creating an illusion of pain. This phenomenon, also called the "thermal grill illusion of pain" (TGIP), was described more than a century ago by Thunberg [29] and characterised during the first part of the XXth century [3]. It has been reinvestigated recently using modern techniques because of its potential value for studying pain mechanisms and the interactions between nociceptive and thermal sensory systems [4,8,11,17,19,22,25]. Painful sensation evoked by normally non-painful stimuli is reminiscent of thermal allodynia often observed in pathological conditions; thus, the investigation of TGIP may also have clinical implications.

Recent studies demonstrated that stimulation with a thermal grill, with temperatures well below the heat and cold pain thresholds, is capable of producing a

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painful burning sensation in a large proportion of healthy volunteers [4,8,22,25] although a subpopulation (25–30%) of subjects are less responsive [4,22]. Additionally, the occurrence and intensity of paradoxical pain was directly related to the magnitude of the difference in temperature between the warm and cold bars of the grill [4].

The neurophysiological basis of this paradoxical pain remains unclear. Consistent with the thermosensory disinhibition theory of pain [12,13], TGIP may result from a reduced level of inhibition of the nociceptive systems normally exerted by cold afferents. Alternatively, it may depend on the convergence and addition of the activity of adjacent cold and warm afferents on CNS multireceptive neurones [4,19].

We recently demonstrated for the first time that the thermal grill paradoxical pain could be modified pharmacologically [22]. We showed that intravenous injection of a low (sub-anaesthetic) dose of ketamine selectively reduced the intensity of the paradoxical pain, without affecting normal thermal (heat and cold) painful or non-painful sensations. By contrast, injection of the opioid receptor antagonist naloxone did not affect either the paradoxical or normal pain. Thus, the thermal grill paradoxical pain involves the glutamatergic systems, acting through the *N*-methyl-D-aspartate (NMDA) receptors, but not the tonic endogenous opiodergic systems. Moreover, the marked selectivity of ketamine action suggests that some of the mechanisms involved in TGIP are similar to those involved in pathological pain (inflammatory or neuropathic), in particular, hyperalgesia/allodynia phenomena which respond preferentially to NMDA antagonists [7,16,18,20].

Here, we further investigated the neuropharmacological mechanisms involved in TGIP, which could represent a new experimental model for testing analgesics. We analysed the effects of intravenous administration of morphine, on normal (physiological) and paradoxical pain evoked by a thermal grill in healthy volunteers in a randomised, double-blind, placebo-controlled, cross-over study.

2. Methods

This study was performed in a group of paid healthy volunteers following the approval by the Ambroise Paré hospital Ethics Committee. Participants were fully informed about the experimental procedures and gave written consent.

2.1. Equipment

Thermal stimuli were produced using a thermode designed and built by SEICER (Mouy, France) [4,22]. The thermode was composed of six bars (1.2 × 16 cm) covered with a copper plate, spaced 2 mm apart for thermal isolation; temperature was controlled by thermoelectric Peltier elements (three per bar). The temperatures of alternate (even- and odd-numbered) bars were controlled independently between 5 and 50 °C to generate various combinations of temperatures (i.e. patterns of the "thermal grill"). Thermistors placed in each bar provided continuous feedback of the thermode–skin interface temperature (resolution ±0.3 °C).

2.2. Study design

The study design was a randomised, double-blind, placebo-controlled, cross-over trial. Each volunteer participated in three experimental sessions separated by one week. During each session, volunteers randomly received an intravenous (iv) injection of one of the three treatments: 0.025 or 0.1 mg/kg of morphine or placebo (saline). The volume and infusion rate for the placebo was similar to those used for the active drug. Infusions were prepared by a nurse who was not otherwise involved in the experiment. Paradoxical pain was measured 5 min after the non-blinded iv administration of naloxone (0.4 mg).

2.3. Experimental procedure

All the experiments were performed at room temperature (21 °C), and thermal stimuli were applied to the palm of the right hand. The volunteers were asked to put their hand on the grill, perpendicular to the long axis of the bars, for 30 s.

For each experimental session, we recorded the following variables before (control period) and 20 min after the end of administration of morphine (0.025 or 0.1 mg/kg) or placebo (saline):

(i) The cold pain threshold and the heat pain threshold, using a staircase algorithm. Even-numbered bars were kept at a neutral temperature, while the temperature of the odd-numbered bars was changed randomly (either increased or decreased) by steps of 3 to 0.5 °C. Subjects had to report whether they perceived each stimulus as painful or not. Temperatures were changed by 3 °C following negative responses and by 0.5 °C following the first painful stimulus; successive stimuli were changed (increased or decreased) by 0.5 °C until the first non-painful sensation was reported.

(ii) The combination of thermal stimuli producing paradoxical pain. Paradoxical painful sensation was defined as a painful sensation evoked by a combination of warm and cool stimuli at 4 °C above cold pain threshold or 4 °C below heat pain threshold, respectively. These parameters were based on our previous study [4]. Then, the mean intensity of paradoxical pain determined at two