Abstract

Rationale: Associative tolerance to the analgesic effects of morphine is most pronounced when morphine is paired with a distinctive context at a long interdose interval (IDI). In contrast, morphine administered at a short IDI promotes the development of non-associative tolerance and disrupts the acquisition of associative tolerance. The impact of IDI on the development of associative tolerance to opioids other than morphine has not been investigated previously.

Objectives: This research examined associative and non-associative tolerance to the analgesic effects of fentanyl in rats. Cross tolerance for these two forms of tolerance with morphine (mu-receptor agonist) and U50,488H (kappa-receptor agonist) analgesia was also investigated.

Methods: Animals were given eight fentanyl injections (0.10 mg/kg) paired or unpaired with a distinctive context at either a 3-h (short) or 96-h (long) IDI. Subjects were then tested for tolerance in the distinctive context using the tail-flick procedure and dose–response curve methodology.

Results: At the short IDI, animals developed non-associative tolerance to fentanyl that was receptor specific, i.e., cross tolerant with morphine analgesia but not with U50,488H analgesia. At the long IDI, fentanyl-tested animals displayed tolerance that appeared to be controlled primarily by associative processes. This associative form of tolerance was also receptor specific, displaying cross tolerance with morphine but not with U50,488H analgesia.

Conclusions: The impact of IDI on the development of non-associative and associative fentanyl tolerance is consistent with findings obtained with morphine showing that conditions conducive to the development of non-associative tolerance disrupt the acquisition of associative tolerance. The cross-tolerance data, however, did not parallel previous research examining the cross-tolerance profiles of associative and non-associative morphine tolerance.

Key words: Fentanyl tolerance · Cross tolerance · Classical conditioning · Associative · Non-associative · Morphine · U50,488H

Introduction

Tolerance, a decreasing drug response following chronic exposure to the drug, can develop rapidly to many of the actions of opioids (Fernandes et al. 1977, 1982). Tolerance acquired to one drug may also generalize to other drugs, a phenomenon known as cross tolerance (Khanna and Lê 1996). The degree of cross tolerance between opioids is generally believed to depend on the extent to which the drugs’ effects are controlled by common receptor mechanisms. For example, rats tolerant to the analgesic effects of morphine display cross tolerance to analgesia produced by fentanyl (Carter and Tiffany 1996), an opioid that, like morphine, produces effects mediated predominantly by mu-opioid receptors (Maguire et al. 1992). In contrast, morphine tolerance may not generalize to the analgesic actions of the opioid U50,488H, a highly selective kappa-receptor agonist with little affinity for mu receptors (Bhargava et al. 1989; Carter and Tiffany 1996).

Tolerance and cross tolerance phenomena have been used extensively as analytical tools in investigations of opioid neurobiology. This research generally presumes tolerance is a function of mere drug exposure and reflects the activation of the same tolerance processes regardless of exposure parameters. However, it has long been recognized that tolerance can vary, both in quantity and quality, as a result of factors other than frequency and magnitude of exposure. Perhaps one of the most important of these is the discovery that morphine tolerance can come under the associative control of stimuli paired with morphine delivery (Siegel 1975).

Siegel (1975) proposed that distinctive environments paired contingently with morphine administration can become conditioned stimuli. Such stimuli elicit conditioned responses that counteract the direct effects of...
morphine. Tolerance develops as these conditioned responses grow stronger over the course of repeated drug-environment pairings. It is well established that classical conditioning processes are responsible for many examples of morphine tolerance (Baker and Tiffany 1985; Goudie and Demellweek 1986; Siegel 1989; Poulos and Cappell 1991). However, not all instances of tolerance can be explained in terms of classical conditioning (Baker and Tiffany 1985). As one example, animals can acquire substantial tolerance to morphine when the drug is administered via an implanted morphine pellet (Advokat 1981). This regimen of chronic morphine exposure does not permit the contingent pairing of distinctive environmental cues with drug delivery. Consequently, tolerance produced with these procedures appears to be controlled by non-associative processes.

Tiffany et al. (1992) produced evidence that acquisition of associative and non-associative tolerance is moderated by the inter-dose interval (IDI) of morphine administration. In this research, rats were given multiple administrations of moderately high doses of morphine either systemically paired or unpaired with a distinctive context at either a short (6 h) or long (96 h) IDI. Rats exposed to morphine at the long IDI developed substantial associative tolerance; this tolerance was highly context specific and displayed robust retention over a 30-day interval. In contrast, rats given morphine at the short IDI developed substantial non-associative tolerance; this tolerance displayed no contextual specificity and decayed completely at the 30-day retention test. These results were in line with other research showing that conditions supporting the development of one form of tolerance (associative or non-associative) interfered with the development of the other form (Dafters et al. 1988; Tiffany and Maude-Griffin 1988; Dafters and Odber 1989; Carter and Tiffany 1996; Cox and Tiffany 1997).

One advantage of this long and short IDI procedure is that it allows for the production of relatively pure forms of either associative or non-associative tolerance while holding parameters of drug and context exposure constant across the two IDI conditions. As an illustration of the importance of distinguishing between these two types of tolerance, Carter and Tiffany (1996) found that the profiles of morphine cross tolerance with mu- and kappa-receptor agonists differed as a function of the associative or non-associative nature of the tolerance. In this research, non-associative morphine tolerance was receptor specific, displaying cross tolerance with fentanyl (mu-agonist) but not with U50,488H (kappa agonist). However, associative tolerance was cross tolerant with both fentanyl and U50,488H. The general pattern of results suggested that associative and non-associative tolerance were subserved by different tolerance processes. This conclusion runs counter to theories of learned tolerance that assume associative tolerance reflects the conditioned expression of the adaptations responsible for non-associative tolerance (Baker and Tiffany 1985; Poulos and Capell 1991). Moreover, these findings emphasize the value of differentiating associative and non-associative tolerance in investigations of the neurobiology of opioid function.

All of the research examining the impact of IDI on the development of associative and non-associative tolerance has been conducted with morphine. Furthermore, although conditioned tolerance phenomena have been studied extensively over the past 25 years, all research on associative tolerance to the analgesic effects of opioids has also been restricted to morphine. Fentanyl, a potent synthetic analgesic that is highly mu-selective (Maguire et al. 1992), should produce a revealing analysis of the generality of associative tolerance phenomena that have been identified with morphine. Given that the analgesic actions of fentanyl and morphine appear to be mediated via mu-opioid receptors, it might be expected that the tolerance and cross-tolerance profiles of associative and non-associative fentanyl tolerance would duplicate those produced by morphine. However, a consideration of the comparative pharmacology of fentanyl and morphine suggests that these two opioids might not produce the same pattern of tolerance and cross-tolerance effects. For example, fentanyl displays greater specificity for the mu receptor than morphine (Emmerson et al. 1994). Consequently, morphine may be more likely than fentanyl to initiate tolerance processes mediated by non-mu receptor systems (Bilsky et al. 1996). Further, fentanyl has greater intrinsic efficacy than morphine at the mu receptor (Magnan et al. 1982; Adams et al. 1990; Walker et al. 1994). Several studies have suggested that the magnitude of tolerance and cross tolerance that develops with mu opioids is related inversely to the intrinsic efficacy of the opioid (Brase 1986; Stevens and Yaksh 1989; Craft and Dykstra 1990; Young et al. 1991; Paronis and Holtzman 1992, 1994). For example, Paronis and Holtzman (1992) reported that rats receiving continuous infusion of fentanyl produced no evidence of analgesic tolerance on the tail-flick test, whereas chronic infusion of morphine yielded substantial tolerance.

The present study examined the tolerance and cross-tolerance profiles of fentanyl administered paired or unpaired with a distinctive context at a short or long IDI. This research investigated the generality of the influence of IDI manipulations on associative and non-associative tolerance that have been established with morphine (Tiffany and Maude-Griffin 1988; Tiffany et al. 1992; Carter and Tiffany 1996; Cox and Tiffany 1997). Furthermore, this research explored whether the profile of cross-tolerance effects obtained with morphine (Carter and Tiffany 1996) generalized to fentanyl.

Materials and methods

Subjects

The subjects were 532 experimentally naive Male Holtzman rats (Sprague-Dawley, Madison, Wis.) approximately 100 days old on the test day. The animals were housed individually in wire-mesh cages in a colony room, maintained on a 12-h/12-h light/dark cy-