Pentobarbitone, but not propofol, produces pre-emptive analgesia in the rat formalin model

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SUMMARY

Injection of formalin into the hindpaw of a rat induces a biphasic response in pain-related behaviours, such that C-fibre activation during phase 1 triggers a state of central sensitization characterized by a longer lasting phase 2. As the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) may participate in processing of nociceptive inputs, we hypothesized that pentobarbitone and propofol, i.v. anaesthetics with known GABA agonist properties, would interfere with development of central sensitization and thereby modify the phase 2 hyperalgesic response. Pentobarbitone administered i.v. before injection of formalin produced dose-dependent suppression of phase 2, even though animals had recovered from anaesthesia, whereas it had substantially less effect when given after phase 1 had resolved. Picrotoxin, a GABA antagonist, reversed the effect of pentobarbitone on phase 2 pain behaviour but was itself a mild analgesic. In contrast, propofol had no effect on phase 2 formalin-induced pain behaviour. Thus we conclude that pentobarbitone, but not propofol, produced pre-emptive analgesia in this model, presumably by suppressing noxious stimulation-induced central sensitization via activation of GABA receptors. (Br. J. Anaesth. 1994; 72: 662–667)

KEY WORDS


Accumulating evidence indicates that noxious stimulation sufficient to activate C-fibre afferents produces hyperexcitability of central nociceptive neurones and that this central sensitization or facilitation contributes to amplification and prolongation of subsequent pain [1, 2]. Moreover, most animal experiments demonstrate that preventing the development of central sensitization by administering an analgesic or anaesthetic before noxious stimulation (i.e. providing "pre-emptive analgesia") suppresses the development of long-lasting pain [1, 3].

However, not all anaesthetics are analgesics and in particular there is controversy about whether barbiturates and propofol have analgesic properties [4]. Although laboratory [5] and clinical [6] studies have demonstrated that barbiturates are hyperalgesic agents with regard to acute pain, tonic pain seems to be pathophysiologically different from acute pain [2] and both pentobarbitone and propofol have properties that suggest they may favourably influence processing of tonic noxious somatosensory inputs. For example, both agents augment the actions of gamma-aminobutyric acid (GABA) [7, 8], an abundant neurotransmitter in the brain and spinal cord [9] that inhibits discharge of primary afferent fibres [10] and second order nociceptive neurones [11]. In addition, GABA agonists can function physiologically as N-methyl-D-aspartate (NMDA) receptor antagonists [12], an observation relevant to consideration of central sensitization and tonic pain because excitatory amino acids (EAA) are thought to play a crucial role in these processes [2, 3, 13].

Hence, we speculated that GABA-mimetic agents would prevent development of noxious stimulation-induced central sensitization and thereby act as pre-emptive analgesics.

To test this hypothesis, we used the rat formalin model [14, 15], which is a well-characterized experimental paradigm of tonic pain. S.c. injection of formalin into the hindpaw of a rat evokes a progressive, biphasic response in pain-related behaviours (e.g. flinching) [14, 15]. Phase 1 begins immediately after injection, lasts approximately 5 min and is caused predominantly by activation of C-fibre afferents by the noxious peripheral stimulus [1]. In contrast, phase 2 begins about 10 min after injection, lasts 60–90 min and is thought to be the result of EAA-NMDA receptor-mediated central sensitization of nociceptive neurones induced by phase 1 activity [1, 3, 13, 14]. Consequently, block of phase 1 or disruption of central neurochemical processes responsible for sensitization (e.g. by administration of potent analgesics or NMDA receptor antagonists), or both, attenuates the phase 2 hyperalgesic response [1, 3, 13]. Therefore, given the fact that GABA-mimetic agents may influence tonic noxious somatosensory inputs [10–12], we predicted...
that pentobarbitone or propofol administered only during phase 1 would reduce phase 2 pain behaviours even after animals had recovered from anaesthesia.

**MATERIALS AND METHODS**

**Animal preparations**

Studies were performed with the approval of the Institutional Subcommittee on Research Animal Care. Fifty-nine male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN, U.S.A.), weighing 275–325 g, were maintained in a 12-h light–dark cycle (lights on at 07:00) and allowed free access to food and water except during nociceptive testing. To control for known diurnal fluctuations in responsiveness to nociceptive stimuli [16], experiments were performed in randomized order between the hours of 10:00 and 22:00.

A chronic indwelling i.v. catheter was inserted to allow administration of anaesthetics and other agents without disturbing the animal. For this purpose, rats were anaesthetized with 1% halothane in oxygen and placed in the supine position. After local infiltration with 0.25% bupivacaine 0.2 ml, the skin was incised in the supraclavicular area, 2–3 mm lateral to the midline. The right external jugular vein was exposed and cannulated with a sterile catheter (PE-50 tubing, Clay Adams, Parsippany, NJ, U.S.A.) filled with normal saline containing heparin 100 i.u. ml⁻¹. The catheter was inserted s.c. to the interscapular area of the back. After operation, rats were housed in individual cages and allowed to recover for at least 48 h before they were used in the experiments.

Rats were allocated to six anaesthetic groups as follows: pentobarbitone 10 mg kg⁻¹ (n = 5), 16 mg kg⁻¹ (n = 6), 20 mg kg⁻¹ (n = 7) or propofol 5 mg kg⁻¹, 10 mg kg⁻¹ or 20 mg kg⁻¹ (n = 4 per group). In separate preliminary experiments, the largest dose of each anaesthetic reliably produced loss of righting reflex for 15 min, while the smallest doses were sub-hypnotic. Both agents were administered i.v. as a 10-mg ml⁻¹ solution. For administration of pentobarbitone, a solution (Anthony Products, Arcadia, CA, U.S.A.) containing pentobarbitone 65 mg ml⁻¹ and ethanol 10% in water was diluted with 0.9% normal saline. For propofol, the commercially available emulsion preparation (Stuart Pharmaceuticals, Wilmington, DE, U.S.A.) containing pentobarbitone 10 % soybean oil (Sigma) in sterile water. The pH of the solution was adjusted to 7 by addition of hydrochloric acid or sodium hydroxide, as necessary.

Animals were placed in a clear cage bedded thinly with wood chips at least 30 min before the start of the experiment so that they could acclimatize to the new environment. Formalin was injected into the hindpaw 5 min (pentobarbitone and pentobarbitone-vehicle groups) or 1 min (propofol and propofol-vehicle groups) after administration of the anaesthetic or vehicle because this is when loss of the righting reflex occurred after the largest dose of pentobarbitone and propofol, respectively. Formalin 5% was prepared from 37% formaldehyde solution by 1:19 dilution with 0.9% normal saline and injected s.c. in a volume of 50 µl into the plantar surface of the left hindpaw using a 27-gauge needle. Animals were returned immediately to the cage and placed in the supine position so that the time until recovery of spontaneous righting could be noted, and allowed to awaken. Thus animals were awake and conscious when phase 2 pain-related behaviour was assessed. An exception was rats that received the largest dose of pentobarbitone or propofol; these animals remained asleep for the first 5–10 min of the phase 2 portion of the formalin-induced response but were awake thereafter.

Based upon results of these initial studies, we conducted additional experiments. First, to assess if pentobarbitone influenced phase 2 pain behaviour directly, five rats received pentobarbitone 20 mg kg⁻¹ i.v. 5 min after injection of the hindpaw with formalin (pentobarbitone post-formalin group). Hence, as with control rats, these animals were conscious during phase 1 formalin-induced pain. Second, the possible role of GABA_A receptors in pentobarbitone-induced analgesia was investigated by administering the non-competitive GABA_A antagonist, picrotoxin, either 1 or 2 mg kg⁻¹ i.v., together with the largest dose of pentobarbitone (i.e. 20 mg kg⁻¹) 5 min before injection of the hindpaw (n = 5 per group). To control for possible direct effects of picrotoxin on formalin-induced pain behaviour, five additional rats were treated with picrotoxin 1 mg kg⁻¹ i.v. alone. Picrotoxin (Sigma) was dissolved in 0.9% normal saline to a final concentration of 1 mg ml⁻¹. Doses of picrotoxin (a known convulsant) were determined on the basis of separate experiments in unanaesthetized rats, which demonstrated that 1 mg kg⁻¹ i.v. produced a brief (< 10 s) self-limited convulsion in some animals, whereas 2 mg kg⁻¹ i.v. produced prolonged generalized seizure. We assumed the peak CNS effect of picrotoxin would occur during phase 1 of formalin-induced pain as another measure of its effect, namely, convulsion, occurs within 5–10 min of i.v. administration.

**Behavioural observations**

In our analysis, flinching was used as a measure of formalin-induced pain. Flinching is one of the pain-related behaviours of the formalin model and is characterized by spontaneous, rapid, brief shaking or lifting of the paw. Accordingly, each episode of shaking, vibrating or lifting of the paw was counted as one flinch; the total number of flinches of the injected hindpaw were counted and recorded every 5 min for 75 min after injection of the foot. Flinching was chosen as a measure of pain because it is more spontaneous than other formalin pain-related
behaviours (e.g. licking) and, consequently, is thought to be more reliable for this purpose [15].

Statistical analysis

Data from phase 1 (0-5 min after injection of formalin) and phase 2 (10-75 min) responses of the formalin test were considered separately. The mean total number of flinches during each phase was calculated for each group. Furthermore, in order to analyse anaesthetic-induced alterations in the time course of phase 2 flinching, the ratio of the number of flinches of the second half of phase 2 (40-75 min) to that of the first half (10-40 min) was calculated. Statistical analysis was performed with analysis of variance (ANOVA) followed by two sets of Dunnett's test for multiple comparisons. In one set, the control group was compared with each treatment group (11 comparisons) and, in the other, data from the pentobarbitone 20-mg kg\(^{-1}\) group were compared with the pentobarbitone post-formalin, pentobarbitone with picrotoxin 1 mg kg\(^{-1}\) and pentobarbitone with picrotoxin 2-mg kg\(^{-1}\) groups (three comparisons). As two sets of Dunnett’s test were performed, a P value less than 0.025 (= 0.05/2) was considered statistically significant.

RESULTS

Animals that received the smallest dose of pentobarbitone (10 mg kg\(^{-1}\)) or propofol (5 mg kg\(^{-1}\)) were calm and motionless until injection of formalin, but never lost the righting reflex, whereas rats that received the largest dose (20 mg kg\(^{-1}\)) were clinically anaesthetized at the time of injection of formalin and remained so for 14-19 min thereafter. While only one of six rats given pentobarbitone 16 mg kg\(^{-1}\) lost the righting reflex (but only transiently), all animals that received propofol 10 mg kg\(^{-1}\) lost spontaneous righting for approximately 5-8 min. After regaining the righting reflex, rats recovered quickly and were clinically indistinguishable from control animals within 3-5 min. Rats treated with pentobarbitone 20 mg kg\(^{-1}\) were the exception; in these animals, slightly insufficient weight-bearing on ambulation was observed for about 30-40 min after injection of formalin.

S.c. injection of formalin to unanaesthetized rats resulted in a highly reproducible, biphasic increase in flinching behaviour of the injected paw (fig. 1). The characteristic phase 1 (0-5 min) and phase 2 (10-75 min) responses were clearly present in both control groups (i.e. propofol-vehicle and pentobarbitone-vehicle groups). As flinching behaviour in the two control groups was nearly identical, data from the groups were pooled for the purpose of subsequent analysis (table I). Pentobarbitone increased phase 1 flinching, although this effect was not dose-dependent (table I, fig. 1). In contrast, propofol produced a biphasic dose-response; the smallest dose (5 mg kg\(^{-1}\)) enhanced phase 1 flinching whereas larger doses attenuated it (table I, fig. 2).

Pentobarbitone and propofol affected phase 2 flinching behaviour differently. Propofol did not alter either the total number or the time course of phase 2 flinches compared with unanaesthetized control animals (fig. 2). In marked contrast, pentobarbitone produced dose-dependent suppression of phase 2 flinching; pentobarbitone 16 mg kg\(^{-1}\) and 20 mg kg\(^{-1}\) decreased flinching by 45% (P < 0.01) and 69% (P < 0.01), respectively, while 10 mg kg\(^{-1}\) had no effect (table I, fig. 1). Moreover, pentobarbitone changed the time course of phase 2 flinching; of the total flinches observed during phase 2, pentobarbitone-treated animals had fewer flinches during the second half, whereas in control animals, flinching was distributed equally throughout phase 2.

### TABLE I. Effect of anaesthesia on formalin-induced flinching behaviour. Data are mean (SEM) of 4-7 animals per group (see Methods). The control group represents pooled data from free pentobarbitone-vehicle and four propofol-vehicle treated rats. Numbers in parentheses are percentage change in flinches from the corresponding pooled control value, with enhancement or suppression indicated by a plus or minus, respectively. 2nd/1st ratio = Number of flinches that occurred during the second half of phase 2 (40-75 min) divided by that of the first half (10-40 min). *P < 0.05, **P < 0.01, compared with the control group (ANOVA and Dunnett’s test); †P < 0.05, ††P < 0.01, compared with pentobarbitone 20-mg kg\(^{-1}\) group (ANOVA and Dunnett’s test)

<table>
<thead>
<tr>
<th>Group</th>
<th>Phase 1 (0-5 min)</th>
<th>Phase 2 (10-75 min)</th>
<th>2nd/1st ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.83 (0.12)</td>
<td>0.73 (0.10)</td>
<td>0.21 (0.09)</td>
</tr>
<tr>
<td>Pentobarbitone</td>
<td>1.24 (0.27) ††</td>
<td>0.89 (0.04)</td>
<td>0.83 (0.12)</td>
</tr>
<tr>
<td>Propofol</td>
<td>0.89 (0.04)</td>
<td>0.83 (0.12)</td>
<td>0.93 (0.14)</td>
</tr>
</tbody>
</table>
PENTOBARBITONE-INDUCED PRE-EMPTIVE ANALGESIA

FIG. 1. Effect of pentobarbitone on formalin-induced flinching behaviour (number of flinches per 5-min period). Pentobarbitone 10 mg kg\(^{-1}\) (O) (n = 5), 16 mg kg\(^{-1}\) (□) (n = 6) or 20 mg kg\(^{-1}\) (△) (n = 7) was administered 5 min before injection of formalin into the foot pad. Control animals (●) (n = 9) received the vehicle for either pentobarbitone or propofol. Pentobarbitone 20 mg kg\(^{-1}\) produced loss of righting reflex for 14–19 min after foot pad injection, whereas smaller doses were sub-hypnotic. Data are mean, SEM.

FIG. 2. Effect of propofol on formalin-induced flinching behaviour (number of flinches per 5-min period). Propofol 5 mg kg\(^{-1}\) (△), 10 mg kg\(^{-1}\) (O) or 20 mg kg\(^{-1}\) (□) (n = 4 per group) was administered 1 min before injection of formalin into the foot pad. Propofol 10 and 20 mg kg\(^{-1}\) produced loss of righting reflex for 5–8 min and 14–19 min after injection, respectively, while 5 mg kg\(^{-1}\) was sub-hypnotic. The control group (●) (n = 9) is the same as that illustrated in figure 1. Data are mean, SEM.

FIG. 3. Effect of timing of administration of pentobarbitone on formalin-induced flinching behaviour (number of flinches per 5-min period). Pentobarbitone 20 mg kg\(^{-1}\) was administered either 5 min before (pre-formalin group (O); n = 7) or 5 min after (post-formalin group (●); n = 5) injection of formalin into the foot pad. The control (●) (n = 9) and the pentobarbitone pre-formalin groups are the same as those illustrated in figure 1. Data are mean, SEM.

FIG. 4. Effect of picrotoxin 1 mg kg\(^{-1}\) (□) (n = 5) or 2 mg kg\(^{-1}\) (△) (n = 5) administered simultaneously with pentobarbitone 20 mg kg\(^{-1}\) 5 min before injection of formalin into the foot pad. The control (●) (n = 9) and pentobarbitone 20 mg kg\(^{-1}\) (O) (n = 7) groups are the same as those illustrated in figure 1. Data are mean, SEM.

TABLE I. Administration of pentobarbitone before phase 1 was critical for maximal suppression of phase 2 pain behaviour because treatment after phase 1 with 20 mg kg\(^{-1}\) was much less effective in attenuating phase 2 flinching than giving the same dose before phase 1 (−23% vs −69%, respectively; \(P < 0.01\)) (table I, fig. 3).

The analgesic effect of pentobarbitone on phase 2 pain behaviour was reversed partially by simultaneous administration of picrotoxin; there were more flinches during phase 2 in rats given pentobarbitone 20 mg kg\(^{-1}\) with picrotoxin 1 mg kg\(^{-1}\) or 2 mg kg\(^{-1}\) than in animals that received pentobarbitone 20 mg kg\(^{-1}\) alone, although only the effect of picrotoxin 2 mg kg\(^{-1}\) was statistically significant (\(P < 0.01\)) (table I, fig. 4). This reversal of pentobarbitone-induced analgesia cannot be explained by hyperalgesic or antanalgesic effects of picrotoxin, as picrotoxin 1 mg kg\(^{-1}\) itself actually reduced phase 1 (48%; \(P < 0.01\)) and phase 2 (40%; \(P < 0.01\)) flinching proportionally (table I).

DISCUSSION

This study provides the first behavioural evidence that two i.v. anaesthetics with known GABA\(_{A}\) agonist properties, propofol and pentobarbitone, have differential effects on noxious stimulation-induced central sensitization. Propofol, even in large doses, did not influence the facilitatory state that developed after formalin-induced noxious stimulation. In contrast, provided it was administered before the critical acute phase (phase 1) of noxious stimulation, pentobarbitone suppressed, in a dose-dependent manner, central sensitization-induced pain behaviour (phase 2), even after animals had recovered from anaesthesia. In addition, as it was antagonized by picrotoxin, a non-competitive GABA antagonist that blocks GABA\(_{A}\) receptor-associated chloride ionophores [17], the effect of pentobarbitone on central sensitization appears to be mediated, at least partially, by GABA\(_{A}\) receptors. Thus we conclude that pentobarbitone, but not propofol, produced pre-emptive analgesia in this model, in part via GABA\(_{A}\) receptor mechanisms.
It is important to note that this analgesic effect is unlikely to be the result of a non-specific action of pentobarbitone (e.g. sedation), because rats that received pentobarbitone 20 mg kg$^{-1}$ after injection of formalin were more sedated during phase 2 but had nearly 2.5 times more flinches during this period than rats treated with the same dose 10 min earlier, before injection of formalin (table I, fig. 3). Moreover, suppression of flinching did not correlate temporally with hypnosis—sedation or predicted concentrations of drug. First, pentobarbitone 16 and 20 mg kg$^{-1}$ suppressed flinches during the latter part of phase 2 (i.e. 25–75 min after injection of formalin) when rats were awake, but had no effect when rats were asleep or still sedated (i.e. 15–20 min after formalin). Second, propofol did not reduce flinching, even though rats that received the largest dose were asleep for the first 5–10 min of phase 2. Third, other studies have demonstrated that inhalation of 0.25% isoflurane through the entire experimental period does not influence flinching in phase 2 [18]. Collectively, therefore, these data indicate that the pre-emptive analgesia produced by pentobarbitone in this model cannot be explained by a non-specific action and that the timing of administration relative to the noxious stimulus is critical.

Agents that produce pre-emptive analgesia in the formalin model of tonic pain and central sensitization can be distinguished by their effects on phase 1 pain-related behaviour. Some, such as opioids and local anaesthetics [3, 15], suppress phase 1 and also phase 2 pain behaviour. As the phase 1 portion of formalin-induced pain is caused by C-fibre activation, the assumption is that these analgesics block input of afferent noxious inputs into the central nervous system (CNS) and thereby prevent central sensitization from being initiated. In contrast, other agents, including NMDA receptor antagonists such as MK-801, suppress phase 2 pain behaviour but have only modest effects on phase 1 [3, 13] and, as such, are presumed to selectively disrupt excitatory amino acid—NMDA receptor-dependent neurochemical events that mediate and maintain central sensitization. The pre-emptive analgesic effect of pentobarbitone observed in this study was analogous to that of NMDA antagonists, in that pentobarbitone suppressed phase 2 pain behaviour while not reducing, or even enhancing, phase 1 flinching. Because picotoxin reversed this effect, it appears that pentobarbitone inhibits central sensitization in part by potentiating GABAergic neurotransmission and mimicking the action of NMDA antagonists. This is not the first evidence that NMDA receptor-dependent neuronal hyperexcitability in the CNS is inhibited by GABA$\alpha$ agonists. Recent experiments showed that thermal hyperalgesia after constriction injury of the sciatic nerve, a phenomenon known to involve activation of spinal NMDA receptors, is exacerbated by intrathecal administration of the GABA$\alpha$ antagonist, bicuculline [19], and that long-term potentiation, a form of NMDA-mediated facilitation in the hippocampus, is also enhanced by GABA$\alpha$ receptor block [20].

The observation that pentobarbitone produced pre-emptive analgesia does not necessarily contradict evidence that systemically administered barbiturates are hyperalgesic or not analgesic [6]. Studies showing barbiturate-induced hyperalgesia [5, 6] used short, phasic noxious stimuli, whereas the current study used a model of prolonged, tonic pain and central sensitization. These differences in the nature of the noxious stimulus are important because the pathophysiology and central modulation of tonic pain are different from those of acute or phasic pain [2]. Indeed, our data support the concept of a hyperalgesic effect of pentobarbitone on acute pain as phase 1 formalin flinching, which is an acute pain response caused by activation of C-fibre nociceptive afferents, was enhanced by pentobarbitone. On the other hand, as intrathecal administration of pentobarbitone produces modest antinociception in a model of phasic pain (i.e. the tail flick test [5]), barbiturate-induced hyperalgesia may actually be the net effect of inhibition at the spinal level and facilitation or disinhibition supraspinally. Such opposing spinal and supraspinal effects could also account for distortion of the time course of phase 2 flinching produced by pentobarbitone; at the time flinching is enhanced or suppressed least (i.e. phase 1 and early phase 2, respectively), supraspinally disinhibited pain may prevail because the concentration in the brain is high, whereas later, as the concentration of pentobarbitone in the brain decreases, its spinal inhibitory—analgesic action may become evident. In any case, despite enhancing the behavioural response to acute, C-fibre afferent-mediated pain, pentobarbitone ameliorates longer lasting pain behaviours that are mediated by central facilitation.

Unlike pentobarbitone, propofol lacks pre-emptive analgesic properties. This difference is not easy to explain as both agents are similar, in that they are general anaesthetics with known GABA$\alpha$ agonist properties [7, 8, 17]. But the drugs may differ in their non-GABAergic actions. Pentobarbitone is much more potent than propofol, for example, in reducing the fractional open time of the human voltage-activated sodium channel [21]. An alternative explanation, and one we consider to be more likely, is that pentobarbitone and propofol may act on different forms of the GABA$\alpha$ receptor. This hypothesis assumes that GABA$\alpha$ receptors are heterogeneous, which seems to be the case. The GABA$\alpha$ receptor is an oligomeric complex consisting of five of 16 different protein subunits, with each subunit exhibiting a distinct regional distribution within the brain and spinal cord [17]. Consistent with the multiplicity of GABA$\alpha$ receptor subtypes is the fact that radioactive ligand-binding studies demonstrate a similarly heterogeneous distribution of binding sites for various GABA$\alpha$ agonists [22]. However, it is premature to conclude that GABA$\alpha$ receptor heterogeneity accounts for the different effects of pentobarbitone and propofol on tonic pain and central sensitization because it is not known if pentobarbitone and propofol bind to different GABA$\alpha$ receptor subtypes [17] and, more importantly, if different GABA$\alpha$ receptor subtypes mediate different cellular functions [9].

Although formalin-induced pain is presumably analogous to postoperative pain, extrapolation of
these results to the clinical situation requires caution. First, the stimuli are different; formalin pain is caused primarily by peripheral tissue inflammation [14], whereas surgical pain has both inflammatory and neuropathic components [2]. Second, species differences may exist [14]. Third, postsurgical pain generally follows a far more protracted time course than that of formalin-induced pain, whereas the duration of pre-emptive analgesia may be short-lived. For example, in a recent human study that compared the effects of infiltration of the skin with lignocaine either before or after cutaneous thermal injury, pre-emptive analgesia lasted for only 70 min after injury [23]. Nevertheless, this study has shown that a barbiturate may ameliorate the development of protracted pain and central sensitization and that such effects outlast the duration of clinical anaesthesia. This is obviously complex because agents with apparently similar anaesthetic actions (i.e. pentobarbitone and propofol) may not be equally effective analgesics. In conjunction with data from our previous study that showed that nitrous oxide is a pre-emptive analgesic in the rat whereas halothane is not [24], it becomes increasingly clear that not all general anaesthetic agents are capable of preventing central neural changes that contribute to the development of long lasting pain.

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REFERENCES


