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Antinociceptive Properties of Propofol: Involvement of Spinal Cord γ-Aminobutyric Acid$_A$ Receptors

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ABSTRACT

In this study, we investigated the interaction of propofol (a compound used widely as an intravenous anesthetic) with γ-aminobutyric acid$_A$ (GABA$_A$) and *delta* opioid receptors at the level of the spinal cord. Nociceptive thresholds were measured in rats through the use of electrical current testing (ECT) and tail-flick latency. Full recovery from sedation occurred 36.3 ± 1.7 min (mean ± S.E.M.; $n = 20$) after 40 mg/kg propofol i.p. Forty minutes after administration, there was residual antinociception when assessed by ECT but not when assessed by noxious heat. The ECT antinociceptive effects of propofol at tail but not neck sites were suppressed by intrathecal injection of the GABA$_A$ antagonists bicuculline and SR-95531 and the *delta* opioid antagonist naltrindole. These results suggest that there is an interaction between propofol and antagonists at receptors in the caudal segments of the spinal cord responsible for tail innervation. Antagonist dose-response curves were compared with those for suppression of intrathecal midazolam-induced antinociception. All intrathecal antagonists reversed the antinociceptive effect of propofol with the same dose-response curves as those previously obtained for suppression of the effect of intrathecal midazolam. We conclude that propofol, when given intraperitoneally, produces antinociception in rats through an interaction with spinal GABA$_A$ receptors. This combination leads to activation of a spinal cord system involving a *delta* opioid receptor; the same mechanisms involved with midazolam-induced spinal antinociception.

Several commonly used general anesthetics, sedatives and anxiolytics (barbiturates, steroid derivatives, alcohols, benzodiazepines and inhalational anesthetics) possess the ability to modulate GABA$_A$ receptors in the central nervous system (Lambert *et al.*, 1995). GABA is the most widely distributed and abundant inhibitory neurotransmitter in the central nervous system. It activates either the chloride-linked GABA$_A$ or the second-messenger-coupled GABA$_B$ receptor (Yeh and Grigorenko, 1995). There is a substantial amount of evidence to suggest that supraspinal GABA$_A$ receptors are important sites for the pharmacological action of many of the nonvolatile and volatile general anesthetics and sedatives (Jones *et al.*, 1995). GABA has also been implicated in the spinal cord control of nociception (Nadeson *et al.*, 1996), but the precise role of the GABA$_A$ receptor in analgesia remains unresolved.

Molecular biological studies have identified the GABA$_A$ receptor as a macromolecular complex. It consists of five subunits with many similarities to the nicotinic acetylcholine receptor complex. Five types of subunit have been described: *alpha*, *beta*, *gamma*, *delta* and *rho*, and multiple variants for each of these classes have been identified (*alpha*, 3*beta*, 2*gamma*, 1*delta* and 2*rho*). Cloning studies have shown that a number of combinations of these subunits may play a role in GABAergic neurotransmission in the central nervous system (Olsen and Tobin, 1990; Tobin *et al.*, 1991; Wafford *et al.*, 1993). The GABA$_A$ receptor complex contains a number of distinct binding sites for ligands, including GABA, benzodiazepines, barbiturates, picrotoxin and *t*-butylbicyclophosphorothionate (Sieghart, 1992).

Propofol [2,6-diisopropylphenol (Diprivan)], a sterically hindered phenol derivative, has become used widely as an intravenous anesthetic. This drug is unrelated structurally to any other general anesthetic and is the most short acting of the commercially available intravenous agents. Studies have suggested that propofol produces anesthesia by acting at GABA$_A$ receptors (Jones *et al.*, 1995; Sanna *et al.*, 1995). A study by Hales and Lambert (1991) showed that propofol potentiated the amplitude of membrane currents elicited by the local application of GABA. These results are consistent with biochemical data showing that propofol increases [^{3}H]GABA binding and GABA-induced Cl^- flux while decreasing [^{35}S]*t*-butylbicyclophosphorothionate binding in rat brain through a bicuculline-sensitive mechanism (Sanna *et al.*, 1995). The early evidence indicated that modulation of GABA$_A$ receptors by propofol resembled the action of other general anesthetics such as barbiturate and steroid derivatives. However, in recent studies, Concas *et al.* (1991, 1992)

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ABBREVIATIONS: ECT, electrical current threshold test; GABA, γ-aminobutyric acid; i.p., intraperitoneal; i.t., intrathecal; TFL, tail-flick latency; %MPE, percentage of the maximal possible effect.

identified a binding site for [^{3}H]propofol in rat brain that differs from either the steroid or barbiturate recognition sites

Studies have shown that positive modulation of the $GABA_A$ receptor in the spinal cord can cause antinociception *in vivo* (Edwards *et al.*, 1990; Nadeson *et al.*, 1996). No *in vivo* studies investigating the role of propofol and $GABA_A$ receptors in spinal cord have been reported. In the present study, we investigate the interaction of propofol injected intraperitoneally with $GABA_A$ receptors at the level of the spinal cord. We used two $GABA_A$ antagonists (bicuculline and SR-95531) injected i.t. to investigate this interaction. These results suggested the same spinal $GABA_A$ receptors were responsible for i.p. propofol antinociception as those involved with spinally mediated antinociception after i.t. midazolam (Goodchild *et al.*, 1996). Spinal *delta* opioid receptors are also involved with midazolam-induced antinociception. We therefore investigated the involvement of spinal cord *delta* opioid receptors with propofol-induced antinociception by attempting to suppress the effects with the *delta*-selective opioid antagonist naltrindole.

Methods

This work was carried out with the permission of the Monash University Standing Committee on Ethics in Animal Experimentation (SCEAE Project No. 93017). In all experiments, attention was paid to ethical guidelines for the investigation of experimental pain in conscious animals (Zimmerman, 1983)

Surgical techniques. Male Wistar rats (weight, 180–200 g) were anesthetized with halothane in oxygen-enriched air ($FiO_2 = 0.4$) and a Portex catheter (i.d., 0.28 mm; o.d., 0.61 mm) was implanted under aseptic surgical conditions into the lumbar subarachnoid space to lie adjacent to lower lumbar and sacral segments of the spinal cord as previously described(Edwards *et al.*, 1990).

After recovery from general anesthesia, the animals were observed for normal movement and behavior; if there was any evidence of neurological damage, they were killed immediately. If there was no neurological damage, lidocaine solution (2%; 10 μl) was injected down the catheter to test for correct i.t. position; correct placement in the i.t. space was assumed if the animal became paralyzed in the hindlimbs within 30 sec of this local anesthetic injection. This test was performed immediately after i.t. cannulation and recovery from general anesthesia and also after each experiment Thus, we were confident that all drugs injected down the catheter were introduced into the lumbar subarachnoid space. A minimum period of 12 hr elapsed between catheter implantation and nociceptive testing.

Test for recovery from sedation. Twenty rats (180–200 g; 10 with and 10 without i.t. catheter) were tested for the presence of the righting reflex and competency to perform the Rotarod test. These tests were used to assess the time taken for full recovery from sedation after an i.p. injection of 40 mg/kg propofol (Diprivan; ICI, Melbourne, Victoria, Australia). The rats were naive with no previous exposure to the Rotarod test. They were placed on the Rotarod accelerator treadmill (Ugo Basile 7650 accelerator Rotarod, Ugo Basile, Varese, Italy) set at the minimal speed for two training sessions of 1 to 2 min at intervals of 30 to 60 min. After this conditioning period, the animals were placed onto the Rotarod at a constant speed of 25 rpm. As the animal took grip of the drum, the accelerator mode was selected on the treadmill (*i.e.,* the rotation rate of the drum was increased linearly at 20 rpm every minute thereafter). The time was measured from the start of the acceleration period until the rat fell off the drum; this was the control (pretreatment) performance time for each rat. The maximum running time was 30 sec. This test was performed on each rat four times with an interval of 30 min between each run. The mean performance time was calculated as an average of the last three control performance times.

The animals were then injected i.p. with propofol (40 mg/kg). The time taken for the animal to lose and regain the righting reflex was recorded. Once the animal had regained the ability to turn over from the supine to the prone position, it was placed on the Rotarod with the test parameters used in the control (pretreatment) period. The time taken for the animal to achieve its own mean performance time was recorded. Because there was no significant difference in the sedative profile between rats with and those without an i.t. catheter (see Results), the results from all 20 rats were combined to calculate an average recovery time. In subsequent experiments on age- and weight-matched rats, we waited for full recovery from the sedative effect of i.p. propofol for a period equal to this average plus 1 S.D. of the mean before continuing with nociceptive testing. Thus, all nociceptive threshold measurements made in subsequent experiments after i.p. propofol were made in rats that would show no signs of sedation or anesthesia ($P < .05$).

Nociceptive tests. Experiments were performed on 38 rats with chronically implanted lumbar subarachnoid catheters. The animals were placed in a restrainer that was covered to exclude distracting sights and sounds. Nociceptive thresholds were measured with ECT and the TFL as previously described (Edwards *et al.*, 1990; Nadeson *et al.*, 1996).

The ECT was measured at two skin sites, tail and neck, to show spinal effects of an i.t. drug (a change in the tail threshold with no change in the neck threshold) (Edwards *et al.*, 1990; Nadeson *et al.*, 1996). These changes were standardized as a ratio of control (predrug administration) as previously described (Nadeson *et al.*, 1996; Serrao *et al.*, 1989b). The TFL was expressed as %MPE with the cutoff time set at 15 sec to avoid damage to the tail. Both ECT and TFL were measured every 5 min, and the order of tests was TFL, tail ECT and then neck ECT.

Measurement of antinociceptive effect of propofol. ECT and TFL were assessed every 5 min until three stable consecutive control readings had been obtained. An i.p. injection of propofol 40 mg/kg ($n = 10$) was then administered, and rats allowed to recover from the effect of propofol for 40 min (the mean recovery plus 1 S.D. assessed by the Rotarod test in the previous group of age- and weight-matched rats). Nociceptive values were then measured every 5 min for 60 min (fig. 1, protocol 1).

The time-response relationships for the antinociceptive effects of i.p. propofol was investigated by recalculating each reading (Y) by dividing it by the mean of the three control (before i.p. propofol) readings for that experiment (X1–X3). All readings from all the rats for each particular time were then combined, and the mean ± S.E.M. value was calculated.

Experiments using antagonist. The involvement of spinal cord $GABA_A$ and *delta* opioid receptors with the antinociceptive effect of i.p. propofol was investigated in 38 rats with chronically implanted i.t. catheters. Experiments were performed on each rat once daily, up to 6 successive days. These animals were placed in a restrainer as above, and protocol 2 in figure 1 was followed. Nociceptive thresholds using ECT (neck and tail) were measured every 5 min until three consecutive stable readings had been obtained at each skin site. Propofol (40 mg/kg i.p.) was then given, and the rats remained in the restrainer. After full recovery from propofol-induced sedation, the residual antinociceptive effects were assessed before and after i.t. administration of bicuculline methiodide (Sigma Chemical, St. Louis, MO), SR-95531 (Research Biochemicals, Natick, MA) or naltrindole HCl (Research Biochemicals) (see protocol 2). The volume of the antagonist injected i.t. was 5 μl. This was chosen so that spread of the drug in the cerebrospinal fluid was minimized and its effect would therefore be restricted to the lumbosacral spinal cord; all antagonists were also dissolved in a slightly hyperbaric 6% dextrose solution for the same reason. To confirm this restriction of the drug effect, ECT was measured at both skin sites every 5 min. A change in the tail ECT after i.t. drug without a change in the neck ECT would indicate that the action of the drug was confined to the caudal segments of the spinal cord responsible for tail innervation.

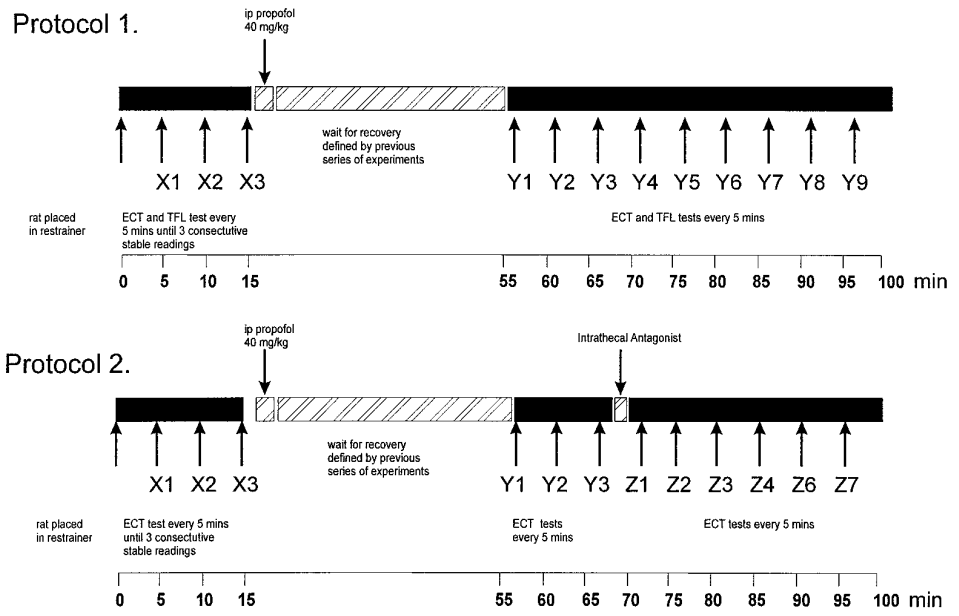

Fig. 1. Two protocols for the experiments in this study. Protocol 1 was used to study the antinociceptive action of 40 mg/kg propofol alone. Protocol 2 was used to assess the interaction of the same dose of propofol with $GABA_A$ receptors at the level of the spinal cord. X1–X3, control period before drug; ECT and TFL measurements. Y1–Y3, propofol (40 mg/kg) alone; ECT and TFL measurements. Z1–Z3, nociceptive thresholds measurements after i.t. injections of antagonists bicuculline, SR-95531 and naltrindole

A range of doses of antagonist were used: bicuculline (1×10^{-12} to 5×10^{-11} mol), SR-95531 (1×10^{-12} to 5×10^{-11} mol) and naltrindole (5×10^{-11} to 5×10^{-8} mol). The effect of the antagonists was calculated as a percentage suppression of the response to propofol alone (mean of Y1 + Y2 + Y3 in protocol 2, fig. 1) using the following equation:

$$\% \text{ Suppression} = \frac{R - r}{R - 1} \times 100$$

where R represents the mean response to propofol alone, and r represents the individual response to propofol in the presence of a dose of antagonist. This was calculated for both neck and tail electrodes. The values thus obtained for each dose of antagonist were combined to calculate mean ± S.E.M. values, which were used to construct an antagonist dose-response curve. These antagonist dose-response curves were compared with antagonist dose-response curves for the same antagonist obtained previously (Goodchild *et al.*, 1996; Nadeson *et al.*, 1996) for the suppression of antinociception induced by i.t. midazolam.

Controls. Experiments conducted in which 5×10^{-11} mol bicuculline ($n = 6$), 5×10^{-11} mol SR-95531 ($n = 6$) or 5×10^{-8} mol naltrindole ($n = 6$) was administered i.t. but without prior i.p. propofol. This was done to determine whether these compounds had any effects on ECT or TFL when given alone.

Statistical analysis. All statistical comparisons between groups were made using Student's unpaired t test or one-way analysis of variance as appropriate. A value of $P < .05$ was considered statistically significant. ED_{50} values were calculated by applying a nonlinear regression to each line using the STATISTICA computer program.

Results

All animals exhibited positive lidocaine tests after each experiment, indicating that the drugs injected down the catheters had been given into the i.t. space. No rat showed overt signs of neurological damage during the series of experiments by either loss of motor power or spontaneous occurrence of anesthesia in the tail.

Recovery from sedation after i.p. propofol. Propofol (40 mg/kg i.p.) caused no loss of righting reflex, but it did cause decreased performance in the Rotarod test. Table 1 shows the time (mean ± S.E.M.) taken to lose and recover performance in the Rotarod test after i.p. propofol (40 mg/kg) for a group of normal rats ($n = 10$) and rats with i.t. catheters ($n = 10$). There was no significant difference in the recovery times between rats with and without i.t. catheters. In pooled data for the two groups, full recovery from sedation measured by the Rotarod test occurred at 36.3 ± 1.7 min (mean ± S.E.M.) after i.p. propofol. In subsequent experiments, all nociceptive readings were taken 40 min (36.3 min + 3.6 min, which is 1 S.D. from the mean) after i.p. propofol.

TABLE 1

Time taken to recover from sedation and regain Rotarod coordination in a group of rats with and without intradwelling lumbar subarachnoid catheters

	Onset of sedation	Regain of Rotarod coordination
	min	
Rats with indwelling i.t. catheters ($n = 10$)	8.5 ± 1.0	37.5 ± 1.8
Rats without indwelling i.t. catheters ($n = 10$)	9.9 ± 0.9	35.0 ± 1.6

Values are mean ± S.E.M. and indicate no significant difference between animals with or without i.t. catheters in recovery time from either sedation or regain of coordination. $P > .05$ by paired t test.

Antinociceptive effect of propofol. Figure 2 shows time-response curves for the antinociceptive effect of propofol assessed using ECT (measured at neck and tail) and TFL. Propofol produced a rise in electrical current threshold in the tail ($R = 2.26 \pm 0.27 \times$ control; mean ± S.E.M., $n = 6$) and in the neck ($R = 2.09 \pm 0.27 \times$ control; mean ± S.E.M., $n = 6$) without affecting TFL (%MPE = 9.77 ± 9.81; mean ± S.E.M., $n = 6$). The antinociception produced by propofol assessed using ECT was sustained for 60 min (the end of the testing period allowed under ethics committee license) after full recovery from propofol-induced sedation.

Reversal of propofol antinociception by antagonists. All three antagonists produced suppression of the residual antinociceptive effects of propofol in the tail but not the neck. Figure 3 shows one such response as a time-response curve, the mean ± S.E.M. from six experiments in which bicuculline

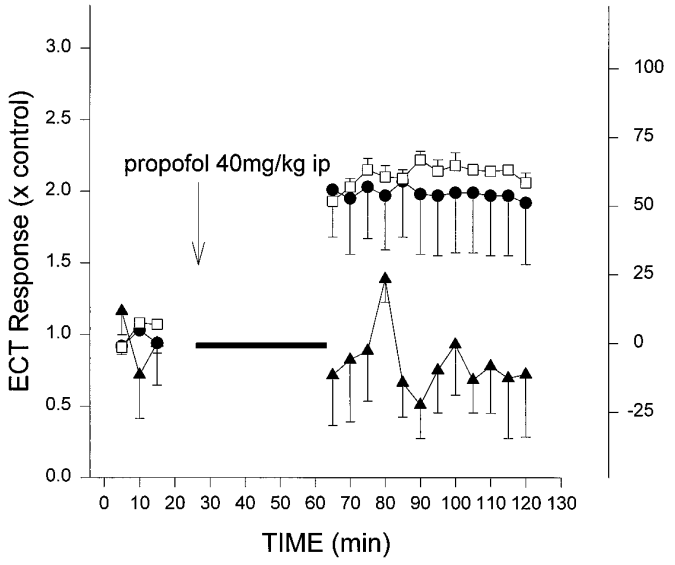

Fig. 2. Time-response curves for the antinociceptive effects of 40 mg/kg propofol i.p. Experiments were performed as in protocol 1. Arrow, time of i.p. injection of propofol. Black bar, period of sedation; ●, neck (ECT); □, tail (ECT); ▲, TFL (%MPE). Values shown are mean ± S.E.M. (n = 6).

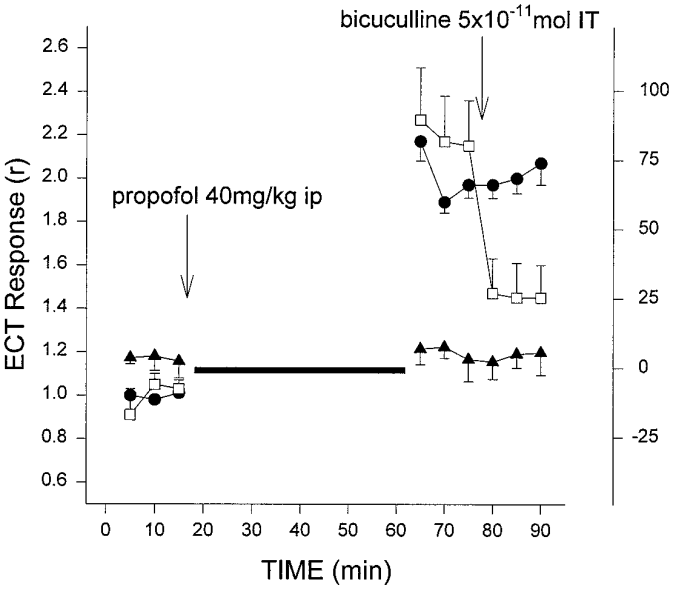

Fig. 3. Time-response curves for the antinociceptive effects of 40 mg/kg propofol i.p. and the effect of 50 pmol bicuculline i.t. Experiments were performed as in protocol 2. Arrows, time of injection of 40 mg/kg propofol i.p. and 50 pmol bicuculline i.t., respectively. Black bar, period of sedation; ●, neck (ECT); □, tail (ECT); ▲, TFL(%MPE). Values shown are mean ± S.E.M. (n = 6).

(5×10^{-11} mol) suppressed the antinociceptive effect of propofol assessed using ECT at the tail skin site but not the neck.

The suppression of the antinociceptive effect of propofol by the three antagonists used was dose related. Figure 4 shows antagonist dose-response curves for all three antagonists in the suppression of spinally mediated antinociception induced by i.t. midazolam shown previously (Goodchild *et al.*, 1996; Nadeson *et al.*, 1996) and by propofol in the experiments reported here. The dose-response curves for the two $GABA_A$ antagonists suppressing the antinociceptive effect of propofol

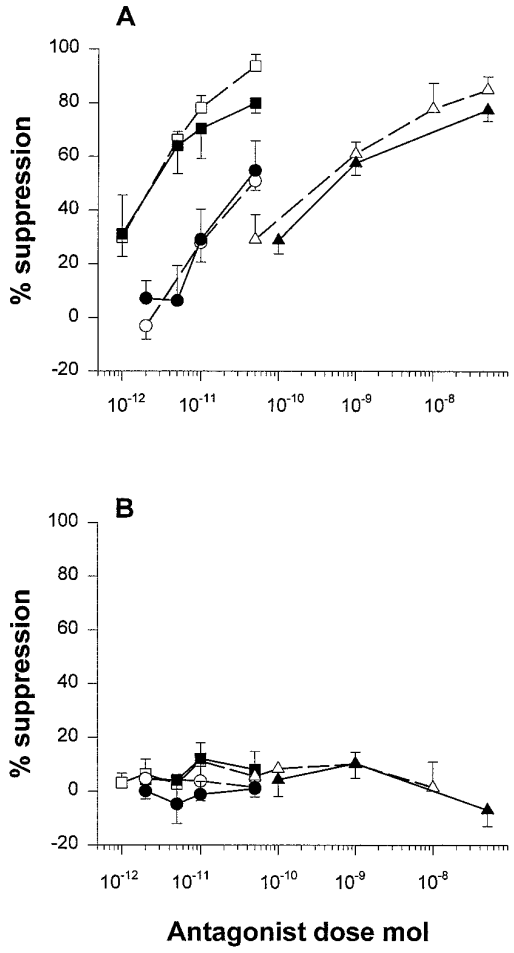

Fig. 4. Antagonist dose-response curves. The suppression by bicuculline (●, ○), SR-95531 (■, □) and naltrindole (▲, △) of the ECT antinociceptive effects of propofol (40 mg/kg i.p.; closed symbols) and i.t. midazolam (47 nmol; open symbols). A, ECT tail skin site. B, ECT neck skin site. ED_{50} values calculated for each curve (STATISTCA) are bicuculline *vs*. midazolam, 4.3×10^{-11} mol; bicuculline *vs*. propofol, 3.4×10^{-11} mol; SR-95531 *vs*. midazolam, 2.2×10^{-12} mol; SR-95531 *vs*. propofol, 2.4×10^{-12} mol; naltrindole *vs*. midazolam, 2.9×10^{-10} mol; naltrindole *vs*. propofol, 4.7×10^{-10} mol.

were different. These curves were fitted to a nonlinear regression model using a statistical computer program (STATISTCA), and the ED_{50} values for these effects were calculated. The curves describing the suppression of the antinociception induced by i.t. midazolam were coincident with those describing the suppression by the antagonist of the i.p. propofol effects (Goodchild *et al.*, 1996; Nadeson *et al.*, 1996).

Controls. Intrathecal injections of bicuculline (5×10^{-11} mol), SR-95531 (5×10^{-11} mol) or naltrindole (5×10^{-8} mol) alone or the vehicles (10% intralipid for i.p. propofol and 6% dextrose for i.t. injections) caused no change in antinociceptive response assessed by either ECT or TFL values at the doses used (table 2).

In each experiment, the ECT values measured during the control period (X1–X3) were compared with the corresponding control measurements in the previous days experiment in the same rat. This revealed no significant difference in either direction as the experimental series progressed. Thus, there were no residual effects of the drugs or the occurrence of neurological damage during the 6-day series of experiments.

TABLE 2

ECT response (r) and TFL (%MPE) in a groups of rats given %6 dextrose i.t., intralipid 10% i.p. or i.t. bicuculline (5×10^{-11} mol) i.t. SR-95531 (5×10^{-11} mol) or i.t. naltrindole (5×10^{-8} mol)

	6% Dextrose i.t. (5 ml)	10% Intralipid i.p. (0.8 ml)	5×10^{-11} mol Bicuculline/6% dextrose (5 ml)	5×10^{-11} mol SR-95531/6% dextrose (5 ml)	50 pmol Nalrindole/6% dextrose (5 ml)
R value ECT (neck) ($n = 6$)	1.06 ± 0.08	0.96 ± 0.03	1.15 ± 0.13	1.15 ± 0.13	1.35 ± 0.18
R value ECT (tail) ($n = 6$)	1.18 ± 0.07	0.98 ± 0.03	1.09 ± 0.11	1.05 ± 0.18	1.22 ± 0.25
%MPE TFL ($n = 6$)	0.70 ± 0.06	1.2 ± 0.06	0.60 ± 0.10	1.6 ± 0.10	0.98 ± 0.08

All values are mean ± S.E.M. and indicate no significant change in threshold. $P > .05$ by paired *t* test.

There were no significant changes in tail or neck thresholds in any animal as the experimental series progressed. In addition, during the daily experiments with antagonists, we compared the magnitude of the response to i.p. propofol (40 mg/kg) before i.t. antagonist with the magnitude of the response in the same animal obtained on other days. We found no significant difference in the magnitude of the response obtainable during the progress of the experimental series. This indicates there was no tolerance or residual drug effects; the preparation and results were both stable and reproducible.

Discussion

Propofol is a commonly used anesthetic that has been shown to enhance GABA-mediated synaptic inhibition in a number of neuronal systems (Hales and Lambert, 1991). In our experiments, an i.p. injection of propofol (40 mg/kg) caused rats to become sedated but not lose consciousness. Full recovery from the sedative effects as measured by the Rotarod test took ~35 min, after which the animals had resumed all normal grooming and feeding behavior. Nociceptive tests were carried out 40 min after the i.p. injection of propofol to assess whether any residual (subanesthetic/sedative) concentrations of propofol caused any antinociceptive effects. Although the rats in which nociceptive thresholds were measured could not be subjected to the Rotarod test while in the restrainer, it is likely that they recovered from the sedative effects of i.p. propofol (40 mg/kg) similarly to the rats in the previous group; they were obtained from the same batch and were the same age and weight. In addition, it was possible to observe them while they were in the restrainer, and they showed no signs of sedation. The residual brain concentrations of propofol (40 mg/kg) that were probably present were therefore not sufficient to cause a noticeable change in conscious level.

After full recovery from sedation, the residual concentrations of propofol produced a rise in both neck and tail ECT values with no change in TFL. This antinociceptive effect was long lasting, and no appreciable reduction was noticed for 50 min after time had been allowed for full recovery from sedation. Because this antinociceptive effect occurred in the absence of any detectable anesthesia or sedation, it can be suggested that the systemic concentration of propofol needed to maintain antinociception is far lower than that required to induce or sustain anesthesia or sedation. However, full recovery and return of nociceptive thresholds to base-line values had occurred by the following day before the next experiment in the series.

In the present study, it is clear that propofol acts similarly to i.t. midazolam in that it has no modulatory role in the nociceptive pathway activated by noxious heat stimulation. Previous studies have shown that the results from a number of different nociceptive tests can yield contrasting results. For example, midazolam, a benzodiazepine, also causes spinally mediated antinociception when given i.t. in our model (Nadeson *et al.*, 1996); this drug causes a rise in tail ECT without a change in TFL. This is in contrast to i.t. fentanyl, which causes antinociception when assessed by both tests (Serrao *et al.*, 1989a). It seems likely that the ECT activates different nociceptive afferents to those stimulated by the TFL test.

An i.t. injection of the $GABA_A$ antagonist bicuculline or SR-95531 caused a dose-dependent reversal of the antinociceptive response to ECT in the tail but not in the neck. This differential effect suggests that there was no rostral spread of the antagonist in the CSF to the cervical levels of the spinal cord or higher because no effect was seen at the neck skin site. It can therefore be concluded that the antinociception produced by propofol is mediated through $GABA_A$ receptors at the level of the spinal cord because both $GABA_A$ antagonists could reverse the tail ECT rise. The antagonists did not reverse the antinociception after i.p. propofol at the neck skin sites. Because the antinociception in the tail site could be reversed by the spinal application of the antagonist, we may conclude that the effects were mediated by spinal cord mechanisms.

In experiments using the *delta* opioid antagonist naltrindole, a similar dose-dependent reversal of the antinociceptive effect of propofol measured by ECT was observed at the tail skin site but not at the neck site. This result suggests that propofol antinociception is also mediated by a spinal *delta* opioid receptor.

When using a particular antagonist, the dose-response curves for suppressing the antinociceptive effect of midazolam given i.t. and propofol given i.p. are the same. This was true for all three antagonists used. When two different antinociceptive agents are suppressed by the same antagonist with the same dose-response relationship and the same ED_{50}, this implies that the drugs are acting either directly or indirectly at the same receptor (Mackay, 1994); that is, the two agents both bind to the receptor or cause release of an endogenous neurotransmitter that binds to the same receptor as the antagonist drug.

This present study suggests that the antinociceptive effect of i.p. propofol is mediated by the same $GABA_A$ receptors as previously described for i.t. midazolam even though the drug is given by a nonspinal parenteral (Goodchild *et al.*, 1996). Propofol, like midazolam, does not bind with *delta* opioid

receptors. However, both drugs must cause a release of endogenous opioid peptides that bind with spinal cord *delta* opioid receptors that were blocked by naltrindole. It is unclear whether propofol binds directly with the spinal cord $GABA_A$ receptors or exerts an indirect action. This could occur by activating brain systems with pathways descending to the spinal cord that then interact with spinal cord $GABA_A$ receptors. To elucidate these questions further, experiments using i.t. administered propofol are required. At present, this is not possible because no suitable vehicle for the drug is available for i.t. injection.

Antinociceptive effects of propofol have been reported in humans (Anker-Moller *et al.*, 1991), and there has been some suggestion from *in vitro* studies that this action occurs *via* modulation of $GABA_A$ receptors. Our studies show that propofol causes antinociception in rats through involvement of the same $GABA_A$ and *delta* opioid receptor observed for midazolam. These mechanisms suggest a possibility for potentiation of conventional *mu* opioid analgesia. Midazolam, however, has to be given i.t. to produce this effect (Yanez *et al.*, 1990). The current evidence suggests that this potentiation occurring at the level of the spinal cord may be achieved with propofol without the necessity of invading the i.t. space. This may be useful in humans, in whom one is always wary of the possibility of neurological damage.

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