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Mechanism of opioid-induced pupillary effects ☆

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Abstract

Objective: This study tested the hypothesis that increased activity in the pupilloconstrictor nucleus by the addition of ambient light and by the administration of fentanyl, sufficient to block pupillary reflex dilation, constricts the pupil of anesthetized patients.
Methods: Pupil diameter was measured in 10 anesthetized patients during noxious stimulation above an epidural block level, in darkness and then with light directed into the left eye. Two measurements were taken from the right eye separated by 5 min. Following the second measurement, fentanyl (1 mcg/kg) was administered and the measures in light and dark were repeated. The effect of light and fentanyl on pupil size and pupillary reflex dilation were analyzed.
Results: An increase in light directed into the left eye constricted the pupil from 2.15 ± 0.38 to 1.87 ± 0.40 mm before fentanyl. Fentanyl did not constrict the pupil either in darkness or light but it did decrease pupillary reflex dilation by 49%.
Conclusions: The miotic pupil during general anesthesia is not maximally constricted. Increased excitation of the pupilloconstrictor nucleus does not account for blockade of pupillary reflex dilation after fentanyl administration during desflurane anesthesia.
Significance: This study does not support the hypothesis that opioid effects on the human pupil are brought about by a direct excitatory action on the pupilloconstrictor nucleus.

Keywords: Opioids; Pupil; Pupillary reflex dilation; Pupilloconstrictor nucleus

1. Introduction

Mu active opioids induce miosis in the awake state and block pupillary reflex dilation (PRD) during general anesthesia but the mechanism of these pupillary effects remains unknown (Larson et al., 1997a,b; Murray et al., 1983). The subject has been studied extensively since Fontana first described the phenomenon in 1765 (Fontana, 2001). Animal studies are of only marginal value because of species differences (Table 1). Because dogs exhibit miosis following large doses of opioids (Martin and Eades, 1961), the current prevalent theory related to opioid effect on the pupil is primarily based upon canine studies (Lee and Wang, 1975).

Lee and Wang anesthetized dogs with nitrous oxide and demonstrated that neurons of the pupilloconstrictor (PC) nucleus increased their firing rate following administration of morphine. The miotic effect was not dependent upon interference with sympathetic control of pupil size, stimulation of the optic nerve, or a local effect on the iris. The authors concluded that opioids stimulate the preganglionic neurons in the PC nucleus (Lee and Wang, 1975). Sharpe and Pickworth noted that micro molar injections of morphine into the periaqueductal gray matter induced miosis in dogs and confirmed that opioid-induced pupillary effects appear to be brought about by effects on structures close to the PC nucleus (Sharpe and Pickworth, 1985). The theory (Gutstein and Akil, 2006) that "opioids directly stimulate the Edinger-Westfal nucleus" (PC nucleus) is primarily based upon these two canine studies.The present study asks whether stimulation of the PC nucleus can explain the block of PRD by opioids during general anesthesia in humans (Fig. 1). Because PRD is thought to occur through inhibition of the PC nucleus (Loewenfeld, 1958), depolarization of the PC neurons *via* increased excitatory input

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Table 1
Species differences in pupillary responses to opioids (Murray et al., 1983; Pickworth and Sharpe, 1985; Larson et al., 1997a)

	Pupil size	Light reflex
Man	Decrease	No change
Cat	Increase	Decrease
Dog	Decrease	Decrease
Rabbit	Decrease	Increase
Rat	Increase	Not studied
Mouse	Increase	Not studied

or by an increase in pacemaker activity might thereby overcome any inhibition brought about by the stimulus.

The experimental plan was to increase PC activity by the addition of ambient light during general anesthesia and note the effect on pupil size and PRD. It was hypothesized that opioids or an increase in ambient light would depolarize the neurons and constrict the pupil. Furthermore, this enhanced excitation of the PC nucleus by light and opioids would depress PRD.

This study was conducted during combined epidural-general anesthesia in anesthetized patients in order to ascertain whether an increase in operating room ambient light directed onto the eye would interfere with the early phase of PRD and thereby confound detection of sensory block levels in these patients (Larson et al., 1993b, 2006).

2. Methods

After approval from the University of California Committee on Human Research, we studied 10 consenting patients undergoing surgical procedures on the lower abdomen (hysterectomy, colon resection, cystectomy) for which combined epidural/general anesthesia was the anesthetic technique. All were American Society of Anesthesiologists physical status 1 or 2, free of eye disease, not morbidly obese, and were not taking drugs other than non-opioid analgesics.

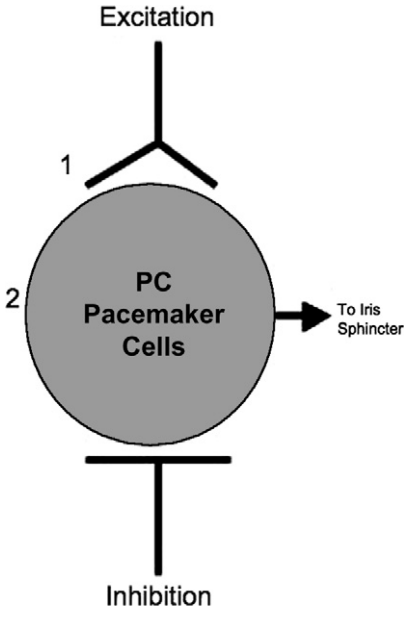

Fig. 1. The tested hypothesis is that increasing the excitation of the PC nucleus brings about the effect of fentanyl on the pupil. This increased activity could by brought about either by an increase in excitatory input (1) or by an increase in pacemaker activity in the PC nucleus (2). The increase in excitation of the PC nucleus would then constrict the pupil and overcome inhibitory inputs such as PRD (shown at the bottom).

Patients were administered a combined epidural – general anesthetic. Lack of pupillary dilation following tetanic electrical stimulation confirmed the efficacy of the sensory block obtained from the epidural local anesthetic. PRD for study purposes was measured above the level of sensory blockade.

Midazolam (1–2 mg) was administered intravenously for sedation and a low thoracic epidural catheter was positioned using loss of resistance to an air or saline filled syringe. Following a negative test dose of lidocaine (3 ml, 1.5% with epinephrine), 10–20 ml of 0.375% bupivacaine was administered via the epidural catheter, the exact dose depending upon the age and height of the patient. Intravenous administration of propofol (1.5–3 mg/kg) induced general anesthesia; rocuronium bromide (0.6–1 mg/kg) was administered to facilitate intubation of the trachea. Desflurane (end-tidal 5%) in air:oxygen (50:50) was administered to maintain anesthesia and rocuronium bromide was given by intermittent bolus to maintain muscular relaxation as determined by a neuromuscular twitch monitor (Digistim III, Neurotechnology, Houston, TX). Opioids were not used prior to the administration of fentanyl during the study.

Hypotension was treated with a fluid bolus of 500 cc Ringers Lactate or blood when indicated. Ventilation was adjusted to maintain end-tidal CO2 between 28 and 38 mm Hg. Body temperature was maintained between 35.5 and 37 °C using a forced air-warming blanket (Bair-Hugger Forced Air-Warming Blanket, Arizant Healthcare, Eden Prairie, MN).

Routine anesthetic monitors including continuous oxyhemoglobin saturation (Nellcor Oximax oxygen sensor, Tyco Healthcare Group, Pleasanton, CA N200) and electrocardiographic monitoring were used in all cases. Oscillometric blood pressure and end-tidal gas concentrations were determined with the S/5 Anesthesia Monitor using an ACX Photometer (Datex-Ohmeda, Inc., Madison, Wisconsin). Core temperature was measured in the distal esophagus using an esophageal stethoscope (Respiratory Support Products, Inc, Irvine, CA).

2.1. Measurement of pupil size and PRD

PRD was measured using a portable infrared pupillometer (Fairville Medical Optics, Inc. Amersham, England) with a resolution of 0.05 mm (Larson et al., 1993a). Stainless steel needle electrodes were placed subcutaneously to deliver a tetanic electrical stimulus for 3 s. Two pairs of such electrodes were used: the lower pair was placed along the flank of each patient approximately two dermatomes