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A model for the preferential delivery of isoflurane to the spinal cord of the goat

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ABSTRACT

To identify the blood supply of the caprine central nervous system, six anaesthetised goats were perfused with coloured suspension into the brachiocephalic artery, the aorta, the iliac artery and the femoral artery. The subsequent distribution indicated that the brain and the main segments of the spinal cord were supplied by the brachiocephalic artery and aorta, respectively. Ten similarly anaesthetised goats then received emulsified isoflurane randomly via either the proximal part of the descending aorta (arterial group) or an ear vein (venous group). In the arterial group, the isoflurane partial pressure (P_{iso}) in femoral arterial blood was almost double the P_{iso} in jugular venous blood. The model showed that preferential delivery of isoflurane to the goat spinal cord in situ was possible and could be used for further research into the mechanisms of anaesthetic action, particularly factors affecting immobility.

Introduction

The mechanism of action and the sites at which volatile anaesthetics produce effects such as immobility, amnesia and unconsciousness, remain unknown (Koblin, 2005). When an anaesthetic is given systemically, it is difficult to determine if an effect is generated by acting on the spinal cord, the brain, or both. To address this problem, models have been developed in which the circulation in a part of the body is bypassed, thereby permitting the anaesthetic agent to be delivered preferentially to, or removed from, that part of the body (Antognini and Schwartz, 1993; Borges and Antognini, 1994; Antognini et al., 2003, 2007).

These investigations may be limited by the severe trauma that is associated with the experimental methods such as cardiopulmonary bypass or transection of the spinal cord. Therefore, a less traumatic model for the preferential delivery of isoflurane to the spinal cord with an intact central nervous system (CNS) and circulatory system is required for the determination of sites of anaesthetic action.

The inhaled administration of volatile isoflurane cannot achieve this goal because isoflurane is distributed equally to the brain and spinal cord. However, emulsified isoflurane administered directly to the circulation of the organ of interest may provide differential concentrations. Previous studies have suggested that isoflurane dissolved in a lipid emulsion produces anaesthesia as effectively as inhaled isoflurane (Eger and MacLeod, 1995; Zhou et al., 2006). Emulsified isoflurane can be administered directly into the circulation and be eliminated via the lungs (Zhou et al., 2003, 2006; Sun et al., 2004; Yang et al., 2006), indicating that this formulation has unusual pharmacokinetic properties. Based upon these findings, we hypothesised that a model permitting preferential delivery of isoflurane to the spinal cord could be developed by infusing emulsified isoflurane into the proximal part of the descending aorta, with pulmonary elimination of isoflurane achieved by mechanical ventilation and a high oxygen flow.

This study was designed: (1) to determine the blood supply of the CNS by injecting coloured suspensions into different arteries and (2) to develop and verify the model by comparing the isoflurane partial pressure (P_{iso}) in the jugular venous blood and in the femoral arterial blood.

Materials and methods

Drug preparation

Emulsified isoflurane was prepared in a fat emulsion (Intralipid, 30% w/v, Huarui) according to a formula developed by our laboratory (Yang et al., 2006; Zhou et al., 2006; Chai et al., 2008). In brief, 1.6 mL of liquid isoflurane (Abbott Laboratories) and 18.4 mL of Intralipid were aseptically stored in a 20 mL glass ampoule; the ampoule was vigorously shaken using a vibrator for 15 min to solubilise the isoflurane into the lipid emulsion. The stability of 8% emulsified isoflurane has been previously reported (Yang et al., 2006).

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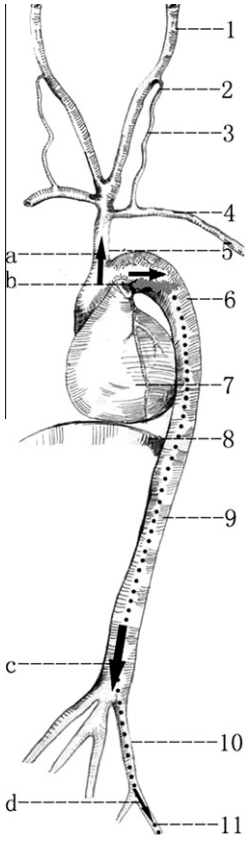

Fig. 1. Schematic diagram of the vascular anatomy of the CNS in the goat (ventral aspect; Yang et al., 2009). 1, carotid artery; 2, occipital artery; 3, vertebral artery; 4, subclavian artery; 5, brachiocephalic artery; 6, thoracic aorta; 7, heart; 8, diaphragm; 9, abdominal aorta; 10, left external iliac artery; 11, left femoral artery. In part 1, the coloured suspensions were injected via a, the brachiocephalic artery, b, the aorta, c, the iliac artery and d, the femoral artery, respectively (shown as black arrows). In part 2, a catheter (shown as black dashed line) was inserted from the femoral artery into the initial section of the aorta for infusing emulsified isoflurane.

Animal preparation

After obtaining approval from the Institutional Animal Care and Use Committee of Sichuan University (Chengdu, Sichuan, China), sixteen goats (*Capra hircus*), aged 20.2 ± 3.2 months (mean ± SD) and 20.72 ± 2.34 kg bodyweight (BW), were randomly divided into two groups with six goats for Study 1, and 10 goats for Study 2.

The goats were anaesthetised with an intravenous (IV) injection of propofol (Diprivan, 1% w/v, AstraZeneca) at a dose rate of 5–8 mg kg^{-1}, followed by suxamethonium chloride (Scoline, Libang) 1–2 mg kg^{-1} IV, all via a catheter inserted into the ear vein. After the palpebral reflex had disappeared, a size 8 Fr. cuffed endotracheal tube coated with 1% dicaine gel (Lining, Nanjin) for endotracheal topical anaesthesia was inserted (Yang et al., 2004).

After intubation, the goats were mechanically ventilated by using a ventilator (excel210SE, Ohmeda), which had a non-return valve in the breathing circuit, with its settings adjusted to maintain the end-tidal carbon dioxide partial pressure in the range 25–35 mmHg (3.3–4.6 kPa). Isoflurane at an inhaled concentration of 1.5–2.5% (vaporiser setting) was used to maintain anaesthesia. During the whole experiment, heart rate, mean arterial pressure, electrocardiograph, lingual pulse oxygen saturation were measured with a multi-parameter monitor (M1167A, Philips). A methane insensitive infrared gas analyser (M1026B, Philips) was used to measure the end-tidal isoflurane concentrations (at a wavelength 10.3–13.0 μm) and end-tidal CO_2. Rectal temperature was measured and maintained at 39 ± 1 °C using a heating lamp and blankets, as needed. Lactated Ringer's solution (10 mL kg^{-1} h^{-1}) was administered through a peripheral ear vein. A rumen tube was placed orally to drain contents.

Study 1: determination of the CNS blood supply

Six goats (3 female, 3 male) aged 19.8 ± 2.9 months and 20.63 ± 2.37 kg BW were prepared as described above. After a thoracotomy was performed and blood vessels exposed, four polyethylene catheters (26 Fr., 66126, Medtronic) were each inserted into one of the following four arteries: (1) the brachiocephalic artery 1 cm distal to its origin; (2) the descending aorta 1 cm distal to its origin; (3) the descending aorta 1 cm before it branches; and (4) the femoral artery 1 cm proximal to its origin, for infusion of coloured suspensions (Figs. 1 and 2).

A suspension of modified polymethyl methacrylate (Cunningham, 1999) was simultaneously perfused through the four catheters by a roller pump, immediately after the proximal ends of the iliac artery and the femoral artery were ligated to avoid mixing different coloured suspensions in the two arteries. To differentiate between individual arterial supply areas, the suspensions were mixed with red, blue, yellow or black coloured oil (Artists' Oil Colors, Winsor and Newton Artists' Materials). The flow rate was regulated to make sure that the perfusion pressure of the suspensions was the same as the mean arterial pressure of each individual goat (about 80 mmHg).

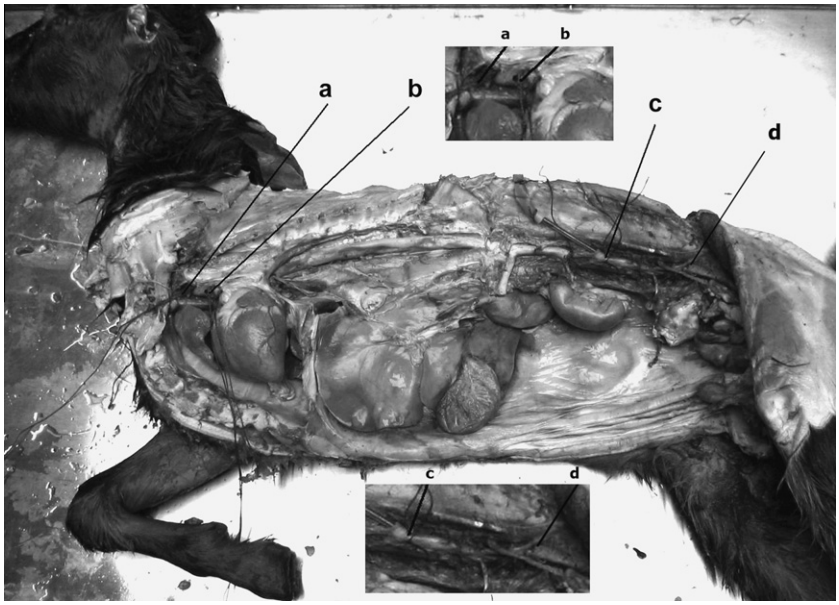

Fig. 2. The median sagittal section of the formalin-fixed goat, showing the positions of four catheters from which the coloured suspensions were infused (a) the brachiocephalic artery 1 cm distal to its origin; (b) the descending aorta 1 cm distal to its origin; (c) the descending aorta 1 cm before it branches, and (d) the femoral artery 1 cm proximal to its origin, for infusion of coloured suspensions.