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Synergism between cocaine and atropine at the caudal ventrolateral medulla of cats

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Abstract

We have previously reported that the anticholinergic properties of cocaine may be important in cocaine induced apneusis. We have studied the effects of the cholinergic muscarinic antagonist atropine (ATR) on cocaine induced apneusis at the caudal chemosensitive areas of the ventrolateral medulla oblongata (CVLM). Experiments were performed in urethane anesthetized and tracheotomized cats with the CVLM surgically exposed. Topical application of ATR (44 mM) to the CVLM produced significant decrements in minute ventilation (V_E) and mean arterial blood pressure (MABP) ($P<0.05$) but the effects on tidal volume (V_T), respiratory frequency (f) and heart rate (HR) were not significant. Administration of cocaine (37 mM) to ATR pretreated animals increased the incidence of cocaine induced respiratory arrest to more than twofold greater than when cocaine was administered in the absence of pretreatment. The ATR pretreated animals that did not experience inspiratory arrest after cocaine were shown to exhibit significant decrements in f and V_E as a consequence of prolonged inspiratory pauses. The reduction in MABP after cocaine in ATR pretreated animals was also significant. These results suggest that ATR enhances the central respiratory toxicity of cocaine by acting synergistically at CVLM chemosensitive sites.

Keywords: Cocaine; Atropine ventral brainstem; Apneusis

Introduction

Cocaine has the capacity to produce hypoventilation by prolonging the inspiratory phase of breathing (apneusis) when administered centrally at the caudal ventrolateral medulla (CVLM) of cats [1–3]. The CVLM is one of three respiratory chemosensitive areas that have

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been described on the ventrolateral medulla of the cat: The rostral area (area M)[4], the intermediate area (area S)[5] and the caudal area(area L) [5,6]. The intermediate and caudal chemosensitive areas are believed to be colocalized with rostral and caudal vasomotor centers, respectively [7]. Several investigations have suggested that atropine sensitive (muscarinic) cholinergic respiratory control mechanisms operate at the CVLM in conjunction with central respiratory chemoreceptor reflexes [8–11]. Acetylcholine and various cholinomimetics appear to stimulate, while atropine (ATR) seems to inhibit, ventilation [8–11]. Although local pretreatment with the cholinomimetic physostigmine ameliorates the hypoventilation and apneusis associated with the administration of cocaine at this site, the cholinomimetic carbachol appears to be ineffective [2]. These findings suggest that an anticholinergic property of cocaine may be involved in cocaine induced apneusis at the CVLM, but the mechanism remains unclear. Cocaine has been reported to have atropine like effects on specific brainstem and cortical neurons, as well as, on cardiac myocytes [12–14]. Therefore, a recent report of lethality of ingesting atropine adulterated cocaine, albeit infrequent, may be attributable to anticholinergic synergism between these drugs [15]. The exacerbation of apneusis and hypoventilation by the synergistic actions of atropine and cocaine reported herein suggests involvement of an atropine sensitive mechanism in cocaine induced apneusis.

Methods

Cats weighing 2.5–4.5 kg were anesthetized with urethane (2.0 g/kg i.v.). The animals were then placed in the supine position and the head stabilized in a Horsely-Clark stereotaxic apparatus. The trachea was cannulated and the CVLM was exposed from pontomedullary boarder to C_1-C_2 as described in a previous work [1]. Catheters were placed into the femoral artery for arterial blood pressure recording and into the femoral vein for fluid administration. Respiratory volume and frequency were measured with a tracheal cannula connected to a low-inertia spirometer (Krogh) with an inductive transducer.The system was connected to a semiclosed circuit from which CO_2 was absorbed while O_2 was continuously replaced. Femoral blood pressure was monitored with a Statham strain gauge transducer (Model P23Db). In some of the experiments, the arterial pressure and respiratory parameters were monitored by a disposable Sen Sym pressure transducer (Cobe) and Model i/a 7321 pneumotachograph (Fleisch) connected to a respiratory flow transducer, respectively. The pressure and airflow signals were logged by a Buxco physiological monitoring system (Buxco Electronics). The systolic blood pressure, diastolic blood pressure, mean arterial blood pressure (MABP), and heart rate (HR) were computed electronically from pressure pulse; tidal volume ($V_{T)}$, respiratory frequency (f), and minute ventilation (V_E) were obtained from pneumotachographically measured airflow waveforms by the Buxco Ls 20 microcomputer software program. The fractional concentration of expiratory CO_2 (F_ECO_2) was measured by either a Model 0151003L Micro-Capnometer (Columbus Instruments) and /or an infrared gas analyzer (Beckman Model LB-2).

In the present studies, cocaine hydrochloride (Sigma) and atropine sulfate (ATR) (Sigma) were dissolved either in artificial (mock) CSF (mCSF) and/or physiological saline and adjusted to physiologic pH 7.4. Previous studies in this laboratory have shown that saline and mCSF do not affect cardiorespiratory function when applied to the CVLM in cats [1]. Drugs