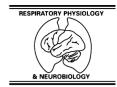


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Supranodose vagotomy eliminates anandamide-evoked cardiorespiratory depression in anaesthetized rats

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Abstract

Respiratory effects of an intravenous injection of anandamide were investigated in 19 urethane-chloralose anaesthetised and spontaneously breathing rats. In 10 neurally intact rats the effects of anandamide were checked to establish appropriate dose of the drug. In the second group, nine rats were challenged with anandamide while intact, following bilateral midcervical vagotomy and after subsequent supranodose vagotomy.

Bolus injection of 1 mg kg⁻¹ of anandamide into the right femoral vein pre- and post-midcervical vagotomy induced in all nine rats prompt apnoea of similar duration: 2.97 ± 0.5 and 3.2 ± 0.4 s, respectively. In post-apnoeic breaths tidal volume decreased below the control level by 25% (*P*<0.01) prior to and by 43.4% (*P*<0.001) after midcervical vagotomy.

Supranodose vagotomy precluded the respiratory response to anandamide. Anandamide-induced decrease in mean arterial blood pressure in nerve-intact and vagotomised rats was abolished by supranodose vagotomy.

Results indicate that the cardio-respiratory depression evoked by anandamide administered via the peripheral circulation requires intact supranodose vagi.

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Keywords: Control of breathing; Anandamide; Apnoea; Vagotomy; Nodose ganglion; Rat

1. Introduction

Anandamide is a natural, endogenous agonist of cannabinoid CB_1 receptors present on the neurones of the central and peripheral nervous system (Freund et al., 2003). They were found in the sympathetic and

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parasympathetic ganglia and on axon terminals of airway nerves (Buckley et al., 1998; Pertwee, 1999; Calignano et al., 2000). Unfortunately, few physiological studies address the contribution of the peripheral CB₁ receptors to the reflex control of breathing. It is generally held that activation of CB₁ cannabinoid receptors with the natural Δ^9 -tetrahydrocannabinol (Δ -9-THC) or synthetic agonists induces cardiovascular depression and markedly impairs ventilation, both in conscious and anaesthetised animals (Doherty et al.,

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1983; Vivian et al., 1998; Schmid et al., 2003). Difficulty with anandamide inheres the fact that it is also the ligand of the vanilloid receptors VR_1 (Zygmunt et al., 1999; Smart et al., 2000). In rats activation of VR_1 receptors by their classical agonist, capsaicin, induces the pulmonary chemoreflex, consisting of apnoea, hypotension, bradycardia and post-apnoeic stimulation of breathing, based mainly on an increased tidal volume (Kaczyńska and Szereda-Przestaszewska, 2000).

Recent study by Lin and Lee (2002) on the effects of anandamide in rats has shown that its administration into the jugular vein evoked hypotension and apnoea of the chemoreflex. In the breaths that followed the apnoea, the tidal volume and the frequency of breathing remained near the baseline. The competitive antagonist of the VR1 receptors eliminated coincident intensive activation of unmyelinated vagal C-fibres by anandamide reported in this paper. Different pattern of the respiratory response evoked by local intraarterial challenge of anandamide into the hindlimb vasculature showed an enhanced ventilation and hypotension, which appeared to be mediated by VR1 receptors (Smith and McQueen, 2001). On the other side, it was shown that the third phase of post-anandamide hypotension was the only phenomenon clearly ascribed to the activation of CB₁ receptors (Varga et al., 1995; Malinowska et al., 2001).

Analysis of the published data provides inconsistent evidence as to the role of the feedback from vagally innervated pulmonary receptors. Respiratory depression due to Δ -9-THC challenge occurred in nerveintact and vagotomised cats (Doherty et al., 1983). On the other side, perivagal capsaicin treatment blocked the response to anandamide in rats (Lin and Lee, 2002). Considering the presence of CB₁ receptors on the vagal pathway and in the nodose ganglia (Buckley et al., 1998), we hypothesised that the nodose ganglia mediate the reflex changes evoked by anandamide.

Present experiments were designed to: (1) characterize the post-anandamide pattern of breathing following an intravenous injection, which has not been addressed; (2) to examine the effectiveness of midcervical and subsequent supranodose vagotomy in precluding anandamide-induced cardiorespiratory effects. The objective of the present study was to evaluate the pattern of cardiorespiratory effects produced by anandamide and its reflex pathway by measuring the ventilatory and blood pressure responses in the intact rats subsequently treated by an infra- and supranodose vagotomy.

2. Methods

Nineteen adult male Wistar rats (195–250 g body weight) were anaesthetised with an intraperitoneal injection of 600 mg kg⁻¹ of urethane (Sigma) and 120 mg kg⁻¹ of α -chloralose (Fluka AG). Additional doses of urethane and α -chloralose were administered intravenously (i.v.), if necessary—dependent on response to applying pressure to a limb joint and the basal heart rate and blood pressure (BP). Rats were placed supine and breathed spontaneously room air. An incision was made in the trachea below the larynx, and the cannula inserted into the caudal end was connected to a pneumotachograph. Femoral vein and artery were catheterized for administration of supplemental anaesthesia and drugs and to monitor blood pressure, respectively.

The vagus nerves in the midcervical region were cleared from the adjacent tissue, removed from the sheath and prepared for section later in the experiment. Rostral vagal trunks were carefully separated from the superior cervical ganglia. The nodose ganglia were dissected free from the surrounding tissue; attention was paid to preserve their blood supply intact. At the last stage of the experiment the supranodose vagi were transected as far from the ganglion as possible, i.e. at least 5 mm distal from its rostral pole.

Ethical approval for the experimental procedures used in this study was obtained from the local animal care committee. All animal procedures were in accordance with NIH Guide for the Care and Use of Laboratory Animals.

Arterial pressure was measured with BP-2 pressure monitor (Columbus Instruments) and mean arterial pressure (MAP) was calculated. Tidal volume signals were recorded from a pneumotachograph (RSS 100HR Research Pneumotach System). End-tidal CO₂ concentration was measured with a capnograph (Engström Eliza plus, Gambro). Electromyogram of the costal diaphragm was recorded with bipolar electrodes, amplified with NL 104 amplifier (Digitimer) filtered and measured with a model AS 101 (Asbit) leaky integrator (time constant = 100 ms). All recordings were registered on an Omnilight 8M 36 apparatus (HoneyDownload English Version:

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