Pharmacological Reports
2011, 63, 448–454
ISSN 1734-1140

Vasopressor and heart rate responses to systemic administration of bombesin in anesthetized rats

Katarzyna Kaczyńska, Małgorzata Szereda-Przestaszewska

Laboratory of Respiratory Reflexes, Mossakowski Medical Research Centre, Polish Academy of Sciences, Pawińskiego 5, PL 02-106 Warszawa, Poland

Correspondence: Katarzyna Kaczyńska, e-mail: kkacz@cmdik.pan.pl

Abstract:
The aim of the present study was to investigate the effects of aortic depressor nerve (ADN) transection, supranodosal vagi denervation (NG vagi cut) and adrenergic receptor blocker treatment on the cardiovascular responses evoked by systemic injection of bombesin.
The cardiovascular effects were studied in spontaneously breathing rats that were (i) bilaterally, midcervically vagotomized (MC vagi cut) and subjected to section of the aortic depressor nerves, (ii) midcervically vagotomized and subsequently vagotomized at the supranodosal level or (iii) midcervically vagotomized before and after pharmacological blockade of α- or β-adrenergic receptors with phentolamine and propranolol, respectively.
An intravenous bolus of bombesin (10 μg/kg) in midcervically vagotomized and ADN denervated animals increased mean arterial blood pressure (MAP) and heart rate (HR). An approximate 20% increase in blood pressure occurred immediately following bombesin injection and lasted for 2–3 min. Augmentation of the heart rate occurred 30–60 s after the bombesin challenge and persisted for more than 10 min. After section of the supranodosal vagi, bombesin failed to induce an increase in heart rate. Blockade of α-adrenergic receptors with an intravenous dose of phentolamine significantly reduced post-bombesin hypertension.
These results indicate that bombesin-evoked increases in blood pressure do not require aortic depressor nerves and supranodosal vagi and are presumably mediated by the activation of peripheral α-adrenergic receptors. Bombesin-induced tachycardia was dependent on an intact supranodose pathway and was amplified by activation of β-adrenoceptors.

Key words:
bombesin, α- or β-adrenergic receptor, aortic depressor nerve, nodosal vagal afferents

Abbreviations: ADN – aortic depressor nerve, HR – heart rate, MAP – mean arterial blood pressure, MC vagi cut – midcervically vagotomized, NG vagi cut – supranodosally vagotomized, NTS – nucleus tractus solitarii

Introduction

Bombesin is a neuropeptide isolated from the skin of the frog *Bombina bombina* and has a higher affinity than its mammalian counterpart, gastrin releasing peptide (GRP), for both bombesin BB_1 and BB_2 receptors [14]. Increasing evidence suggests that endogenous bombesin and its receptors are involved in central and peripheral regulation of various physiological functions and the pathogenesis of several diseases [10]. There is very little information concerning the effects of exogenous bombesin on the cardiovascular system.

Bombesin has been shown to exert cardiovascular action. In an experimental model of bleeding, it was

shown to be very potent in restoring blood pressure in rats and rabbits [11, 17]. Bombesin applied to the cerebral ventricles or administered systemically raised mean arterial blood pressure and altered heart rate in conscious and anesthetized rats [2, 4, 5, 8, 12]. In these studies, the cardiovascular effects of bombesin were evaluated in animals with an intact neuraxis. Most of the authors ascribed these responses to activation of the adrenergic system. However, the type of adrenergic receptor responsible for these effects remains controversial. Some studies have demonstrated that α-adrenergic blockade eliminated bombesin-elicited hypertension and tachycardia [5, 8], whereas others showed the involvement of the -adrenergic pathway [2, 9].

Our recent results have shown that midcervical vagotomy effectively abrogated all respiratory effects of bombesin, but did not affect hypertension, which was similar in magnitude as in vagally intact rats [15]. Therefore, bombesin's effects on cardiovascular responses remain unclear. The present experiments were conducted to determine the potential neural pathways that mediate the cardiovascular effects of bombesin, which occur independently of lung vagal afferents, and to verify whether hypertension and tachycardia are mediated *via* excitation of either α- or β-adrenoceptors. Therefore, we investigated the contributions of aortic depressor nerves, the supranodosal vagi and the adrenergic nervous system on cardiovascular changes evoked by bombesin.

Materials and Methods

Animals and surgical procedures

All animal procedures complied with the NIH Guide for the Care and Use of Laboratory Animals. Ethical approval for the experimental procedures used in this study was obtained from the local institutional review committee. Twenty eight adult male Wistar rats, weighing 200–250 g, were anesthetized with an intraperitoneal (*ip*) injection of 600 mg/kg urethane (Sigma) and 120 mg/kg α-chloralose (Fluka AG). Supplementary doses were administered intravenously as needed based on responses to nociceptive stimuli. Anesthetized rats were placed in the supine position and were allowed to breathe room air spontaneously. The trachea was exposed, sectioned below the larynx and cannulated. A catheter was inserted into the femoral vein for drug administration and supplemental doses of anesthetic. A second catheter was inserted into the femoral artery to monitor blood pressure. Core body temperature was maintained close to 37–38°C with a heating pad.

In both series of experiments, rats were initially midcervically vagotomized. The midcervical vagi were bluntly dissected and sectioned. In the first series of experiment, the aortic depressor nerves (ADNs) were exposed at the area where they join the superior laryngeal nerves. The ADNs were identified as myelinated nerves running parallel and medial to the vagus nerve low in the neck and joining the superior laryngeal nerve close to the nodose ganglia [1, 18]. The ADNs and the superior laryngeal nerves were cut later in the experiment. In the second series of experiment, the nodose ganglia were bluntly dissected from the surrounding tissue, and their blood supply was preserved. The supranodose vagi were sectioned 2 mm distal to the rostral poles of the ganglia before measuring the cardiovascular variables in the midcervically vagotomized rats.

Apparatus and measurements

Tidal volume signals were monitored with a pneumotachograph head attached to the tracheal cannula linked to a Research Pneumotach System (RSS 100 HR, Hans Rudolph Inc., Kansas City, USA) and a computerized recording system (Windows software version 3.07.02, KORR Medical Technologies Inc., Salt Lake City, USA) for measuring and controlling the respiratory parameters.

Arterial blood pressure and heart rate were measured with a BP-2 blood pressure monitor (Columbus Instruments, Columbus, OH, USA). The recordings were registered on an Omnilight 8 M 36 apparatus (Honeywell, Tokyo, Japan).

Drugs

Each drug was prepared fresh from a powder before each experiment, dissolved in physiological saline and injected as a bolus into the femoral vein. The compounds tested included the following: bombesin (Tocris, UK), injected at a dose of 10 μg/kg; propranolol hydrochloride (1 mg/kg; Tocris, UK); and phentolamine hydrochloride (1 mg/kg; Sigma Aldrich,