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Special Issue on Galanin

Role of galanin and galanin(1–15) on central cardiovascular control

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Abstract

Galanin and the N-terminal fragment Galanin(1–15) are involved in central cardiovascular regulation. The present paper reviews the recent cardiovascular results obtained by intracisternal injections of Galanin and Galanin(1–15) showing that: (A) the Galanin antagonist M40 blocks the central cardiovascular responses induced by Galanin(1–15) but not those elicited by Galanin; (B) both Galanin and Galanin(1–15) induce the expression of c-Fos in cardiovascular nuclei of the medulla oblongata with different temporal and spatial profiles; (C) the cardiovascular action of Galanin(1–15), but not Galanin, is mediated by peripheral β-receptor stimulation; (D) and it is demonstrated an antagonistic Galanin/α2-adrenoceptors interaction as well as a differential modulation of central cardiovascular responses of Angiotensin II by Galanin or Galanin(1–15). All these data strengthen the involvement of both Galanin molecules as neuromodulators on central cardiovascular regulation.

Keywords: Galanin; Galanin(1–15); Cardiovascular control; Galanin receptor; M40; Brainstem

1. Introduction

Galanin (GAL) is a 29 amino acids neuropeptide that was originally isolated from the porcine gut (Tatemoto et al., 1983). Both GAL-like immunoreactivity and its specific receptors analyzed by autoradiography and by in situ hybridization show a widespread distribution in the central nervous systems of mammals (Skofitsch et al., 1986; Melander et al., 1986). Until now, three cloned receptor subtypes for GAL GAL-R1, GAL-R2 and GAL-R3 have been described (O'Donnell et al., 1999; Waters and Krause, 2000). These receptors are known to show a higher affinity for GAL than for Galanin N-terminal fragments such as Galanin(1–15) [GAL(1–15)] (Branchek et al., 1998). However, the presence of specific binding sites for this GAL fragment in the central nervous system has been described also in areas lacking [^{125}I]-GAL binding sites (Hedlund et al., 1992). These binding sites have inter alia been shown to be present in the hypothalamus and the brainstem, where a cluster of GAL(1–15) binding sites is located in the dorsal part of the nucleus tractus solitarius (Hedlund et al., 1992). Furthermore, electrophysiological experiments have demonstrated the existence of a GAL(1–15) selective receptor in the hippocampus (Xu et al., 1999).

GAL has been involved in multiple physiological functions (Wynick et al., 2001; Crawley et al., 2002) including the central cardiovascular control functions (Harfstrand et al., 1987; Hedlund et al., 1991). Intracisternal injections of GAL elicit a transient increase of mean arterial pressure (MAP) followed by a rapid decrease. This early increase of MAP appears 5 min after

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the injections but from the 10th min a progressive decrease in MAP is observed. However, a significant tachycardica was observed during the whole 60 min recording period (Harfstrand et al., 1987; Hedlund et al., 1991; Narváez et al., 1994). On the contrary, intracisternal injections of GAL(1–15) induce vasopressor and tachycardic responses that appears early after the injections and were maintained during the whole period of recording (Narváez et al., 1994). Intracisternal co-injections of both Galanin molecules show that GAL(1–15) antagonizes the cardiovascular responses elicited by GAL (Narváez et al., 1994). These effects were also observed with the GAL N-terminal fragment 1-16 but not with GAL C-terminal fragments (Díaz-Cabiale et al., 1998). Furthermore, GAL(1–15) was shown to decrease baroreceptor sensitivity, whereas GAL had no effect in this reflex (Díaz et al., 1996).

Also both Galanin molecules interact differentially with the cardiovascular responses elicited by the activation of central 5-HT_{1A} receptors (Hedlund et al., 1991, 1994; Narváez et al., 1994). Taken together all these data, it may be suggested that both Galanin and its N-terminal fragment 1-15 play a role on central cardiovascular regulation, probably acting through different receptor subtypes recognizing GAL and/or its N-terminal fragments.

In this review, we will summarize the recent data obtained in our laboratory with both GAL and GAL(1–15) that strength their role on central cardiovascular control. The effect of the GAL antagonist M40, the efferent pathways, and the nuclei involved on the cardiovascular responses mediated by GAL and GAL(1–15) have been analyzed. Also, the possible interaction with other neuropeptides and neurotransmitters involved in cardiovascular regulation was also studied.

2. Effect of the specific Galanin receptor antagonist M40 on the central cardiovascular responses of GAL and GAL(1–15)

Many attempts have been made to block the effects of GAL by the use of specific receptor antagonists. These antagonists include M15 [Galanin-(1–12)-Pro-Substance P-(5-11)], M35 [Galanin-(1–12)-Pro-Bradykinin-(2-9)], M40 [Galanin-(1–12)-Pro-(Ala-Leu)2-Ala-amide], C7 [Galanin-(1–12)-Pro-Spantide], M32 [Galanin-(1–12)-Pro-Neuropeptide Y-(25–36)] or galparan [Galanin-(1–12)-Pro-Mastoparan] (Bartfai et al., 1991, 1992, 1993; Wiesenfeld-Hallin et al., 1992; Corwin et al., 1993; Crawley et al., 1993; Langel et al., 1996). Since the chimerical nature of these antagonists they could theoretically interact with other receptors apart from GAL receptors. This is not the case for the GAL receptor antagonist M40, since there is no receptor for its C-terminal fragment. Because of these characteristics M40 was used as the GAL receptor antagonist in these experiments (Narváez et al., 2000).

To investigate the possible modulation of M40 on the central cardiovascular effects of GAL and GAL(1–15), different groups of rats were co-injected intracisternally with a subthreshold dose of M40 (0.1 nmol) and an effective dose of GAL or GAL(1–15).

In Fig. 1, it is shown that after intracisternal injections of GAL(1–15) (3.0 nmol) a significant vasopressor effect ($P < 0.001$ vs. control group) appear early and they are maintained during the whole period of recording. However, after the co-injections of GAL(1–15) with the antagonist M40 the vasopressor response completely disappears (Fig. 1). This blocking effect is highly significant ($P < 0.001$ vs. GAL(1–15) alone) and maintains blood pressure at a similar level as observed in the control group. Together with the vasopressor action, GAL(1–15) increases HR significantly ($P < 0.001$ vs. control group) and the antagonist M40 blocks also the increase of the HR and the response observed is not different from the control group (Narváez et al., 2000).

On the other hand, intracisternal administration of GAL (3.0 nmol) elicit a transient increase of MAP that appears 5 min after the injections and decreases very rapidly reaching a plateau at the 30 min time interval at similar levels to those observed in the control group (Fig. 2). The co-injection with the specific receptor

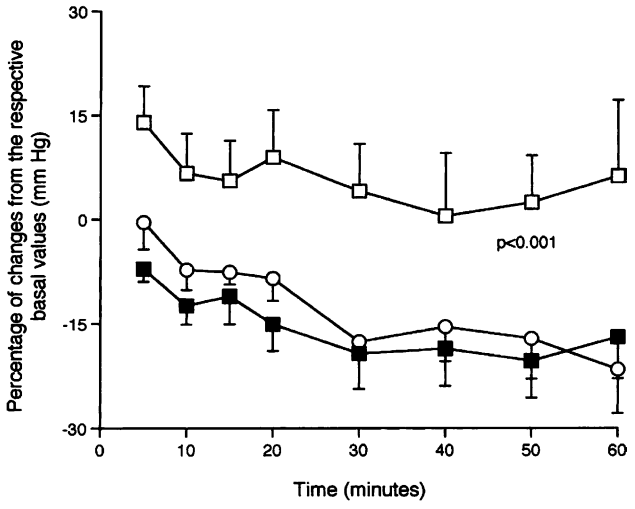

Fig. 1. Effects of intracisternal injections of 3.0 nmol Galanin-(1–15) (open squares) or 3.0 nmol Galanin-(1–15) + 0.1 nmol M40 (black squares) on mean arterial pressure over the 60 min recording period. Open circles represent the control a CSF group. The percentage of changes from the respective basal values are shown as means ±SEM ($n = 7$–8 rats per group). Basal values were: control group, 89 ± 5 mmHg; Galanin-(1–15), 85 ± 3 mmHg; Galanin-(1–15) + M40, 90 ± 10 mmHg. $P < 0.001$ is the significance level of Galanin-(1–15) alone vs. control group and vs. Galanin-(1–15) + M40 group during the whole period of recording (Dunns test) (Narváez et al., 2000).