Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol12Issue3abst005P.pdf

Intravenous Olcegepant Blocks The Sensory Vasodepressor CGRPergic Outflow And Facilitates The Sympathetic Vasopressor Outflow In Pithed Rats

CM Villalón, VH Avilés-Rosas, E Rivera-Mancilla, AH Altamirano-Espinoza, G Manrique-Maldonado, B Villanueva-Castillo. Farmacobiologia, Cinvestav-IPN (Sede Sur), Mexico City, D.F./Tlalpan, Mexico

Systemic vascular tone is modulated by perivascular sympathetic and primary sensory CGRPergic nerves (1). Olcegepant is a selective non-peptide antagonist of CGRP receptors with acute antimigraine properties (2). This study analysed in pithed rats the effect of i.v. olcegepant on: (i) the vasodepressor responses induced by stimulation of the sensory CGRPergic outflow or exogenous α-CGRP; and (ii) the vasopressor responses induced by stimulation of the sympathetic outflow or exogenous noradrenaline.

After pentobarbital anaesthesia (60 mg/kg, i.p.), 70 male Wistar rats (divided into 14 groups, n=5 each) were pithed, artificially ventilated with room air (56 strokes/min; stroke volume: 20 ml/kg) and prepared for spinal stimulation (50 V; 2 ms pulses) of: (i) the sensory vasodepressor CGRPergic outflow (T_9-T_{12}; 0.56-5.6 Hz) during i.v. infusions of hexamethonium (2 mg/kg.min) and methoxamine (10-15 μg/kg.min; to increase blood pressure) (weight: 300-350 g) or i.v. α-CGRP (0.1-1 μg/kg) (1); or (ii) the sympathetic vasopressor outflow (T_7-T_9; 0.03-3 Hz) (weight: 250-280 g;) or i.v. noradrenaline (0.03-3 μg/kg) (3). The carotid artery was cannulated for measurement of blood pressure and heart rate. Before electrical stimulation, animals received i.v. gallamine (25 mg/kg; to avoid muscular twitching). Body temperature was kept at 37°C by a lamp and monitored with a rectal thermometer. Data analysis included 2-way repeated-measures ANOVA+Student-Newman-Keuls test. Statistical significance (*) was accepted at $P<0.05$. Our experiments were approved by our institutional ethics committee (protocol number 507-12).

As shown in Figure 1 (control responses): (i) sensory outflow stimulation and i.v. α-CGRP resulted in frequency-dependent (Fig.1A) and dose-dependent (Fig. 1B) vasodepressor responses; (ii) sympathetic outflow stimulation and i.v. noradrenaline produced frequency-dependent (Figs. 1C, 1D) and dose-dependent (Figs.1E,1F) vasopressor responses. These remained unaltered after 1 ml/kg bidistilled water i.v. (olcegepant vehicle; Figs. 1A, 1B, 1C, 1E). In contrast, i.v. olcegepant (1000 & 3000 μg/kg): (i) blocked the vasodepressor responses to electrical stimulation (Fig.1A) or α-CGRP (Fig. 1B); and (ii) facilitated the vasopressor responses to sympathetic stimulation (Fig. 1D) or i.v. noradrenaline (Fig. 1F).

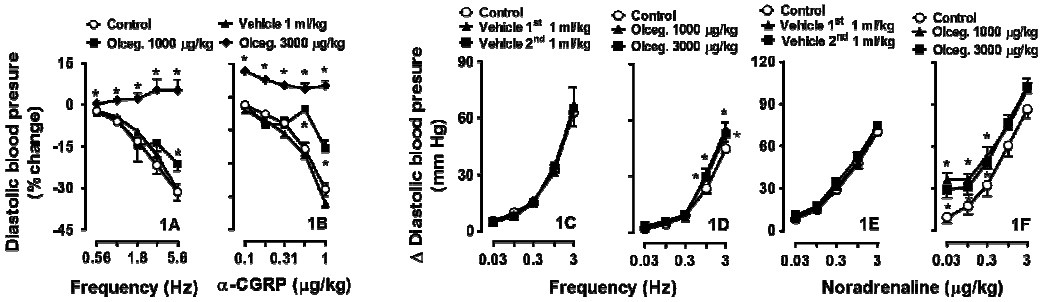

Figure 1. Effect of i.v. vehicle or olcegepant (Olceg.) on changes in diastolic blood pressure.

In conclusion, systemic blockade of CGRP receptors facilitates noradrenergic vasopressor responses.

1. Villalón CM *et al*. (2008). *Br J Pharmacol* **154**: 51-59.

2. Villalón CM and Olesen J (2009). *Pharmacol Ther* **124**: 309-323.

3. Villalón CM *et al*. (1998). *Br J Pharmacol* **124**: 1001-1011.