SCIENTIFIC LETTER

Central α_2 adrenoceptors and the pathogenesis of carotid sinus hypersensitivity

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While the physiology of the normal carotid baroreflex is reasonably well established, the pathophysiology of carotid sinus hypersensitivity (CSH) remains obscure. It has been proposed that central α_2 adrenoceptor upregulation provides the substrate for the changes in baroreflex gain which manifest as CSH.¹ This hypothesis suggests that carotid sinus stiffness resulting from age related cardiovascular disease causes relative diminution of afferent baroreceptor neural traffic, with compensatory brain stem post-synaptic α_2 adrenoceptor upregulation. This physiologic denervation hypersensitivity then causes the overshoot bradycardia and hypotension following carotid sinus stimulation that is clinical CSH. Though widely quoted, this hypothesis has no evidence base, and no attempts have been made to date to test it. If α_2 adrenoceptor hypersensitivity was the major pathophysiological defect in CSH, a centrally active α_2 adrenoceptor antagonist should abolish or attenuate the effects of carotid sinus massage (CSM) in such individuals.^{1,2} In order to test this hypothesis we studied the effects of the central α_2 adrenoceptor antagonist yohimbine³ on the vasodepressor response to CSM in syncopal subjects with CSH, in a randomised, double blind, placebo controlled study, utilising a crossover design.

METHODS

Eighteen consecutive patients with syncope caused by CSH, who had been referred for permanent pacemaker implantation through our syncope facility and had a minimum reproducible vasodepressor response of 20 mm Hg during CSM post-pacemaker, participated in this study. While a 50 mm Hg fall in systolic blood pressure (SBP) during CSM defines vasodepressor CSH,⁴ a previous study has shown that during supine CSM in healthy subjects, mean vasodepression was 19 mm Hg on the right, and 14 mm Hg on the left.⁵ Subjects were studied post-pacemaker implantation so that the fixed cardiac pacing rate avoided the confounding effects of hypotension secondary to variable bradycardic or asystolic

Figure 1 Central α_2 adrenoceptor hypothesis: study design. CSM, carotid sinus massage.

Figure 2 Change in systolic blood pressure (SBP) post-intravenous yohimbine and saline.

responses to CSM. The investigation had local ethical approval. Following informed, written consent, 10 ml solutions of intravenous yohimbine hydrochloride (0.063 mg/kg) and normal saline were infused over two minutes into each subject via antecubital cannulae, on separate days, in random, double blind fashion with a minimum 48 hours between injections to ensure adequate washout of the active drug (distribution half life 0.4–18 minutes, elimination half-life 15–150 minutes) (fig 1).³

Twelve lead ECG and non-invasive beat-to-beat blood pressure measurements (Finapres, Ohmeda, Wisconsin, USA) were then recorded at baseline and during supine, sequential, bilateral and longitudinal CSM (with a one minute interval between episodes) for five seconds before and after each injection. Continuous ECG and blood pressure monitoring occurred throughout the study periods. Time to SBP nadir with CSM was also recorded. The mean differences in vasodepressor response and time to SBP nadir following bilateral CSM before and after saline injection were compared to differences before and after yohimbine injection using an independent sample *t* test.

RESULTS

Of 18 subjects, nine were female and the mean age was 73.9 (8.31) years. None of the subjects were on medications that interacted with α_2 adrenoceptors or yohimbine. Seven (39%) subjects experienced side effects following yohimbine infusion which included tremulousness, anxiety, teeth chattering, and cold sweat; one subject experienced a headache after receiving the placebo. The rise in SBP following yohimbine injection (37 mm Hg) was significantly greater than that following saline injection (15 mm Hg, 95% confidence interval (CI) 8.12 to 35.54; *p* = 0.0037), a difference of 22 mm Hg (fig 2). Vasodepressor responses and time to SBP

Abbreviations: CSH, carotid sinus hypersensitivity; CSM, carotid sinus massage; SBP, systolic blood pressure

Table 1 Vasodepressor response and time to SBP nadir following CSM with saline or yohimbine injection						
Drug	Vasodepressor responses to CSM (mm Hg)			Mean time to SBP nadir (seconds)		
	Pre-injection	Post-injection	Difference	Pre-injection	Post-injection	Difference
Saline n=18	22.22 (16.03 to 28.42)	17.50 (12.10 to 22.90)	4.72 (-2.34 to 1.79)	13.58 (12.28 to 14.89)	12.62 (11.07 to 14.17)	0.77 (1.13 to 2.67)
Yohimbine n=18	25.83 (20.96 to 30.70)	22.80 (17.58 to 28.03)	3.03 (-2.76 to 8.82)	13.86 (12.23 to 15.49)	14.19 (12.21 to 16.17)	-0.48 (-3.12 to 2.16)

Data are expressed as mean (95% CI).
CSM, carotid sinus massage; SBP, systolic blood pressure.

nadir with CSM are detailed in table 1 and fig 3 (vasodepressor responses only).

The mean change in vasodepressor response to CSM before and after saline injection was 4.72 mm Hg (95% CI -2.34 to 11.79), while that before and after yohimbine injection was 3.03 mm Hg (95% CI -2.76 to 8.82) (table 1, fig 3). This difference (1.69 mm Hg) was not significant (95% CI -8.88 to 12.27, p = 0.725). There was no significant difference in the time to SBP nadir following yohimbine and saline injection (difference 1.25 seconds, 95% CI -1.98 to 4.48, p = 0.44) (table 1).

DISCUSSION

We found no evidence of a critical role for central α₂ adrenoceptor upregulation in the pathogenesis of CSH. If the hypothesis were correct, the powerful central α₂ adrenoceptor antagonist yohimbine should have attenuated the vasodepressor response to CSM; it did not. Criticism could be levelled at the small vasodepressor response (less than the usual SBP criteria for vasodepressor CSH), but its previous validation as an abnormal response,⁵ reproducibility and the within subjects control factor afforded by the crossover design, make this unlikely. Furthermore, the use of patients with a pure vasodepressor response to CSM (that is > 50 mm Hg fall in SBP with CSM) may have increased the risk of watershed type neurological complications, particularly given the repeated episodes of CSM in each

patient. Patients with a pacemaker already implanted, controlled for the potentially confounding effects of bradycardia/asystole on blood pressure. O'Mahony suggested pre-medication with apraclonidine before yohimbine injection to ensure only central α₂ adrenoceptor blockade.¹ While the hypertension and other hyperadrenergic side effects experienced by study participants clearly demonstrate the adequacy of central α₂ adrenoceptor blockade, the vasodepressor response to CSM during yohimbine administration was unchanged, arguing strongly against a significant role for these receptors in CSH.

The α₂ adrenoceptor hypothesis, though plausible, remains speculative and without evidential foundations. Adequately powered, replicative studies are needed, as are more detailed neurohistochemical and neuropathological studies. Therapeutic strategies in any disease should ideally be guided by a sound understanding of its pathophysiology; while permanent cardiac pacing is effective in the management of cardioinhibition in CSH, there is no adequate treatment for the vasodepressor component of the disorder. Further work on the underlying pathophysiology of CSH is thus not simply an academic exercise but a clinical imperative.

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Figure 3 Vasodepressor response with carotid sinus massage (CSM) before and after saline or yohimbine injection.