Central $\alpha_2$ adrenoceptors and the pathogenesis of carotid sinus hypersensitivity

S W Parry, M Baptist, J J Gilroy, N Steen, R A Kenny

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 $\alpha_2$ adrenoceptor upregulation provides the substrate for the changes in baroreflex gain which manifest as CSH. 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 $\alpha_2$ 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 $\alpha_2$ adrenoceptor hypersensitivity was the major pathophysiological defect in CSH, a centrally active $\alpha_2$ adrenoceptor antagonist should abolish or attenuate the effects of carotid sinus massage (CSM) in such individuals. In order to test this hypothesis we studied the effects of the central $\alpha_2$ adrenoceptor antagonist yohimbine 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, 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. 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 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).

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 $\alpha_2$ 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...
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 from 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 from 2.34 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 directed at the validity of 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.

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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