Alpha₂-Adrenoceptor Inhibition in Patients with Vibration White Fingers

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Summary: In healthy subjects the physiological vasoconstriction to local cooling has been linked to sympathetic adrenoceptors of the alpha₂-subtype. The present study was designed to determine if the vasoconstriction in response to local cooling in patients suffering from vibration white fingers can be diminished by alpha₂-adrenoceptor inhibition. Six men with vibration white fingers, verified in a cold provocation test, were examined. To study the effect of local skin cooling blood flow was measured with laser doppler technique on the dorsum of dig. II or III. The temperature of the laser doppler probe was regulated by Peltier elements. Temperature could be lowered from 30°C to 20°C within 30s. Measurements were performed before and after local inhibition of the alpha₂-adrenoceptors. This was achieved by the introduction of the selective alpha₂-adrenoceptor inhibitor, rauwolscine, into the finger skin by iontophoresis. During control conditions local cooling consistently resulted in a marked vasoconstriction. Inhibition of the alpha₂-adrenoceptors by rauwolscine completely abolished this effect. The present data indicate that substances inhibiting alpha₂-adrenoceptors may be of therapeutic value in patients with vibration white fingers.

Key words: vibration — blood flow — alpha-adrenoceptors — mechanism — temperature

Introduction

Local cooling augments the vasoconstriction induced by norepinephrine in cutaneous vessels (Vanhoutte and Shepherd, 1970). In isolated canine saphenous veins Flavahan et al. (1985) recently found that this augmented vasoconstriction is dependent on functional adrenoceptors of the alpha₂-subtype. This observation was also shown to be valid for the physiological vasoconstriction in human finger skin in response to local cooling (Ekenvall et al.

1988). The aim of the present experiments was to elucidate if the vasoconstriction in the fingers of subjects suffering from vibration white fingers, i.e. exaggerated vasoconstriction to cooling, can be abolished by inhibition of alpha₂-adrenoceptors.

Subjects and Methods

Methods: The effect of local skin cooling on blood flow was measured with laser

doppler technique (Periflux, Perimed KB, Sweden). The temperature of the laser doppler probe was regulated by Peltier elements controlled by a servo system. Measurements were made before and after local iontophoretic administration of the selective α_2 -adrenoceptor antagonist, rauwolscline. The effect of the blockade was evaluated by comparing vasoconstriction to the α_2 -agonist, B-HT 933, before and after inhibition of the α_2 -adrenoceptors.

Procedure: The subjects were examined in the supine position with the examined hand slightly above heart level. Finger temperature was recorded continuously; and if less than 32°C, the subject was warmed with a blanket to ensure a reasonable vasodilation before the start of the experiment. The laser doppler probe for combined blood flow measurement and local cooling was applied to the dorsal side of the second or third finger on the middle phalanx and the temperature of the probe was set at 35°C. After 15 min of continuous blood flow measurement, the temperature of the probe was suddenly decreased to 20°C and cooling was performed for 30s. The temperature of the probe was then reset at 35°C for 2 min. The cooling warming cycle was repeated three times.

The α_2 -adrenoceptors in superficial skin were then inhibited on the dorsum of an adjacent finger. This was done by iontophoretic administration (current, 400 microampere; time, 12 min) of rauwolscline. For iontophoresis a plastic ring with a diameter of 20 mm with a platinum rod as anode was used. The cathode was a standard ECG electrode on the forearm. The laser doppler probe for combined blood flow measurement and local cooling was then applied within the blocked area and measurements, as described during control conditions, were repeated.

After the cooling procedures, B-HT 933 was introduced iontophoretically (current, 200 microampere; time, 2 min) into the same finger skin areas that were examined earlier to achieve a vasoconstriction mediated by α_2 -adrenoceptor activation. A modified probe holder for the laser doppler was used allowing simultaneous iontophoresis and measurement of skin blood flow (Lindblad et al. 1986).

Subjects: Six men with vibration white finger verified by cold provocation tests (Ekenvall and Lindblad, 1986a) were examined. Informed consent was obtained from all subjects and the protocol of the study was approved by the local Ethics Committee.

Drugs: Rauwolscline HCl (Carl Roth), 10 mmol/l, and B-HT 933 2HCl (azepevole, Boehringer Ingelheim), 10 mmol/l, were used. The concentrations used were determined from earlier experience. All drug concentrations refer to those in the iontophoresis chamber.

Analyses: Mean blood flow was calculated by a microcomputer (Hewlett Packard 9856), during 1 min before and during 10s after cooling (Fig. 1), and during 2 min before and during the fourth and fifth minutes after B-HT 933 administration. The laser doppler gives relative flow values only, and therefore changes in blood flow due to cooling or α_2 -adrenoceptor agonist administration were calculated as a quotient between the blood flow after and before intervention. The mean quotient of the three cooling experiments within the same skin area was used in the statistical analysis.

Statistical methods: Wilcoxon's test for matched pairs (two-tailed) was used with a level of significance of $p < 0.05$.

Fig. 1. Analysis curve of a blood flow recording during local cooling. The decrease in blood flow on local cooling was calculated as $(B/A) \times 100$. For analysis the mean value of three cooling cycles was used. To emphasize the relative nature of the measurements, blood flow values are given as percentages of the full scale deflection of the panel instrument.

Results

In all subjects local cooling from 35°C to 20°C induced a consistent and marked blood flow reduction during control conditions. After alpha₂-adrenoceptor inhibition by rauwolscline, the reaction to cooling was virtually abolished ($p < 0.05$). Fig. 2 gives an example of an original recording and the results are summarized in Fig. 3.

Administration of B-HT 933 induced a marked vasoconstriction in all subjects during control conditions. After alpha₂-adrenoceptor inhibition by rauwolscline, the effect of B-HT 933 was inhibited, $p < 0.05$, (Fig. 4).

Fig. 2. Segments of an original blood flow recording during local cooling without intervention (left) and after inhibition of alpha₂-adrenoceptors (right).

Fig. 3. Decreases in blood flow from local cooling during control conditions (left) and after α_2 -adrenoceptor inhibition (right). Mean values $\pm$ SEM in 6 subjects.

Fig. 4. The effects of B-HT 933 during control conditions (left) and after inhibition of α_2 -adrenoceptors (right). Mean values $\pm$ SEM in 6 subjects.

Discussion

In the present experiments an inhibition of the α_2 -adrenoceptors by rauwolscline was obtained, as evidenced by the reduction of the vasoconstriction induced by the α_2 -adrenoceptor agonist, B-HT 933. Rauwolscline inhibited the vasoconstriction due to local cooling. This extends earlier findings in healthy subjects that vasoconstriction to local cooling is dependent on functional α_2 -adrenoceptors (Ekenvall et al. 1988) to be true also in subjects suffering from vibration white fingers.

It might be argued that the reaction is dependent on an unselective α -adrenoceptor inhibition rather than a selective inhibition of α_2 -adrenoceptors of the α_2 subtype. However, based on earlier experiments this is not likely for several reasons.

1. With the experimental parameters (drug concentration, current, time) used in the present experiment it has been shown (Lindblad and Ekenvall, 1986) that rauwolscline selectively inhibits α_2 -adrenoceptors with no demonstrable effect on α_1 -adrenoceptors.

2. In healthy men selective inhibition of adrenoceptors of the α_1 subtype with doxazosine had only a small effect on cold induced vasoconstriction (which was the reason for omitting α_1 -adrenoceptor blockade in the present study). Furthermore patients with VWF have a reduced sensitivity to α_1 -adrenoceptor agonists (Ekenvall and Lindblad, 1986b) making a contribution of α_1 -adrenoceptors further unlikely.

The concept that α_2 rather than α_1 -adrenoceptors provide a link to vasoconstriction in response to local cooling is also strongly supported by the experiments of Flavahan et al. (1985). Using appropriate pharmacological techniques, they showed in the isolated canine saphenous vein that the increased vasocon-

striction to norepinephrine during cooling disappears after blockade of the alpha₂-adrenoceptors, but not after alpha₁ blockade.

Another possible concern is that the reaction is dependent on basal blood flow, as alpha₂-adrenoceptor inhibition tends to increase basal blood flow. Due to technical limitations in the present set-up blood flow could not be measured during the administration of rauwolscine. To reduce any influence of such a mechanism, the experiments were started with a finger temperature of at least 32°C to ensure that the vessels were reasonably dilated already before antagonist administration, and the sympathetic vasoconstrictor tone was thus as small as possible. The influence of such a mechanism is further made unlikely by the results in a recent series of control experiments (Lindblad et al. 1990). In these experiments, performed in six healthy subjects, a pronounced vasodilation occurred while warming the whole body with a water perfused suit until the finger temperature exceeded 35°C. Even during this condition the vasoconstriction in response to local cooling was unimpeded.

The present finding that vasoconstriction induced by local cooling is inhibited after blockade of alpha₂-adrenoceptors in subjects with VWF suggests a novel therapeutical approach. Drugs with a blocking effect on alpha₂-adrenoceptors may be of possible use to ameliorate cold

reactivity in this disease. The confirmation of such a concept, however, has to await further experiments.

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