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SHORT COMMUNICATIONS

Influence of clonidine-like hypotensive drugs on adrenergic platelet reactions

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In the past several years pharmacological studies have provided evidence for the existence of two types of α-adrenoceptors subclassified as α_1- and α_2-adrenoceptors. These two kinds of α-adrenoceptors differ in their sensitivity to adrenergic agonists and antagonists [1–4]. Recently the adrenaline-induced reactions of human platelets have been shown to be mediated by activation of α-adrenoceptors resembling the α_2-type [4–8]. Clonidine which preferentially activates α_2-adrenoceptors has been described as a partial agonist at adrenergic receptors on the platelets [5, 6, 9]. The clonidine-like hypotensive drugs such as guanfacine, guanabenz and xylazine have been also found to be preferential agonists at presynaptic α_2-adrenoceptors [10–14]. In the present investigations the influence of these agents on platelet aggregation was studied and compared with that of clonidine.

Materials and methods

Substances. Adrenaline (VEB Jenapharm, Jena, GDR); clonidine (VEB Arzneimittelwerk Dresden, GDR); guanfacine (Sandoz, Basle, Switzerland); guanabenz (Wyeth Laboratories Inc., Philadelphia, USA); xylazine (Bayer, Frankfurt, FRG); yohimbine (VEB Arzneimittelwerk Dresden, GDR); ADP (Zellstoffabrik Waldheim, FRG).

Platelet aggregation study. Platelet-rich plasma (PRP) was obtained from venous blood of healthy donors by differential centrifugation. The anticoagulant used was sodium citrate (9 vol. blood + 1 vol. 3.14% sodium citrate solution). By dilution with homologous platelet-free plasma PRP was adjusted to a platelet count of 2.5 to 3 $\times$ 10^8 platelets/ml. Aggregation was measured turbidimetrically at 37°. Before the addition of ADP (final concentration 2 μmoles/l) or adrenaline (final concentration 5 μmoles/l) platelets were preincubated with the test substance for 2 or 3 min, resp. Per cent inhibition of aggregation was calculated by comparing the maximum decrease in optical density of the control with the maximum decrease in optical density of the experimental samples. Each compound was tested in five concentration steps on different (at least 4) PRP.

Results

In contrast to adrenaline, clonidine and the hypotensive drugs at concentrations of 0.1 to 100 μmoles/l did not cause platelet aggregation. Addition of clonidine-like drugs to platelet-rich plasma two min before ADP resulted in an increase in ADP-induced aggregation (Fig. 1). The enhancive effect was especially evident at low ADP concentrations. Adrenaline, however, potentiated aggregation to a greater extent than the clonidine-like drugs. The potentiating effect of the clonidine-like drugs was antagonized by yohimbine, a preferential α_2-adrenoceptor blocker (Fig. 1). Yohimbine alone had no influence on the ADP-induced aggregation.

In studies on the adrenaline-induced platelet aggregation clonidine and related compounds were shown to cause inhibition in a dose-dependent manner. The inhibitory effect was demonstrated by typical aggregation curves (Fig. 2). The concentration–response curves for the inhibition of the adrenaline-induced aggregation showed a parallel shift and the slopes did not vary significantly (Fig. 3). In comparative studies clonidine proved to be the most potent inhibitor followed by guanabenz and guanfacine; xylazine was ten times less effective than clonidine. Since yohimbine and the clonidine-like drugs possess high affinity for the same receptor type, they are assumed to compete for the same receptor sites. After simultaneous application of equi-effective concentrations of yohimbine and one of the clonidine-like drugs aggregation was inhibited to the same extent as after administration of one of the inhibitors.

Discussion

The present findings are consistent with the hypothesis of the existence of α_2-adrenoceptors on platelets. The clonidine-like drugs were found to exhibit a partial agonistic effect on human platelets as it is produced by clonidine. At low concentrations these drugs enhanced the ADP-induced aggregation, at high concentrations they inhibited the adrenaline-induced aggregation. Since the effects on platelet aggregation are antagonized by yohimbine, they

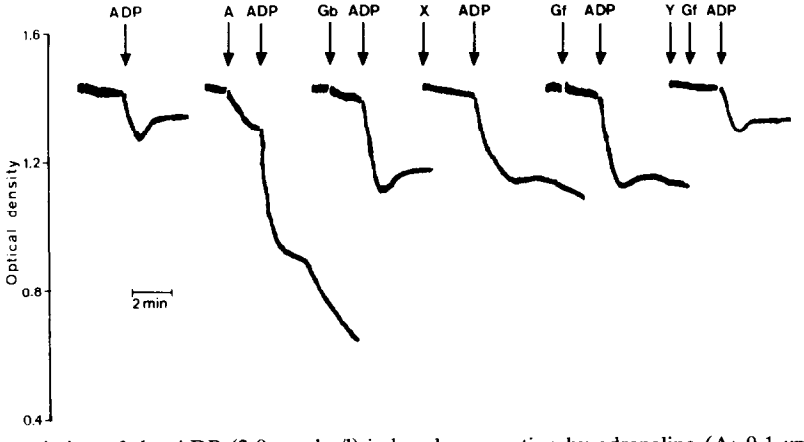

Fig. 1. Potentiation of the ADP (2.0 μmoles/l)-induced aggregation by adrenaline (A: 0.1 μmole/l), guanabenz (Gb: 0.6 μmole/l), xylazine (X: 6.0 μmoles/l) and guanfacine (Gf: 0.6 μmole/l) and inhibition by yohimbine (Y: 0.6 μmole/l). At these concentrations the clonidine-like drugs did not cause inhibition of the adrenaline-induced aggregation.

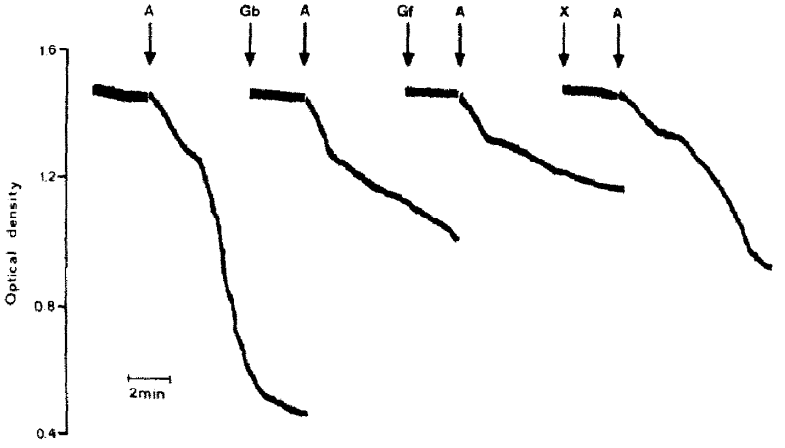

Fig. 2. Inhibition of the adrenaline (A: 5.0 μmoles/l)-induced aggregation of human platelets in citrated plasma by guanabenz (Gb: 6.0 μmoles/l), guanfacine (Gf: 10.0 μmoles/l) and xylazine (X: 30.0 μmoles/l). C: control.

are attributed to an activation of α_2-adrenoceptors. The most potent inhibitor of the adrenaline-induced aggregation was clonidine. In other isolated tissues clonidine has been found to possess a stronger activity towards presynaptic α_2-adrenoceptors than guanfacine and xylazine [10, 14, 15]. In sympathetic peripheral tissues clonidine in dependence on the concentration exerted agonistic and antagonistic effects not only on postsynaptic but also on presynaptic adrenoceptors [16, 17]. At a low biophase level of noradrenaline, clonidine is thought to activate the presynaptic adrenoceptors and to suppress the release of noradrenaline. When the biophase level of noradrenaline is sufficiently high, clonidine competes with noradrenaline and an antagonistic effect results, provided the intrinsic activity of noradrenaline is higher than that of clonidine. In the case of α-adrenoceptors on platelets the same might be true for the dualistic effect of the clonidine-like drugs. However, it has to be taken into account that, similar to the α_1-adrenoceptors, the receptors of the α_2-type may vary in their molecular properties from tissue to tissue and from species to species [17, 18]. Displacement studies with [^{3}H]dihydroergocryptine have shown different dissociation constants of the α-adrenergic antagonists for the α_2-adrenoceptors in different tissues [4].

The aggregation-potentiating effect of the clonidine-like hypotensive drugs possibly occurring at therapeutic doses might be of disadvantage in patients who are at risk from thrombotic disease or in the case of latent transient platelet aggregation. On the other hand, the specific inhibitory effect on the adrenergic platelet reaction may be of therapeutic value in hypertensive states accompanied with thromboembolic complications, particularly when the catecholamine level in blood is elevated, whereby a higher risk of thrombosis exists.

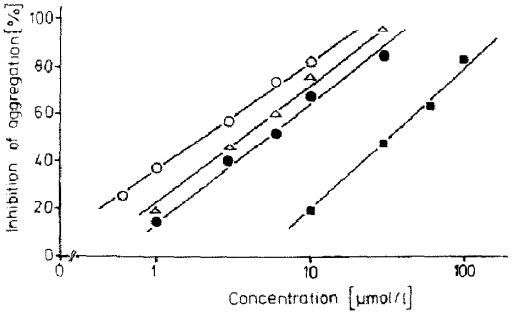

Fig. 3. Concentration-response curves of the inhibitory effect of clonidine (○——○), guanabenz (△——△), guanfacine (●——●) and xylazine (■——■) on the adrenaline-induced aggregation of human platelets (mean values from 4–6 experiments each).

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