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[^{3}H]Noradrenaline-releasing action of vinpocetine in the isolated main pulmonary artery of the rabbit

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Vinpocetine (10^{-6} – 3×10^{-5} M) increased both the resting and the nerve stimulation-evoked release of [^{3}H]noradrenaline from the isolated main pulmonary artery of the rabbit in the presence of uptake blockers (cocaine, 3×10^{-5} M; corticosterone, 5×10^{-5} M), and inhibited the nerve stimulation-evoked postsynaptic response. The resting transmitter releasing action of vinpocetine increased in the absence of cocaine. Exogenously applied (−)noradrenaline [(−)NA] (10^{-6} M) or clonidine (10^{-6} M) inhibited the vinpocetine (3×10^{-5} M)-potentiated [^{3}H]NA release and contracted the circular muscle. The clonidine-induced contraction was abolished by 10^{-7} M prazosin. The inhibitory action of (−)-NA on vinpocetine-potentiated [^{3}H]NA release was partly antagonized by 3×10^{-7} M yohimbine, a preferential α_2-adrenoceptor blocker. In Ca-free Krebs solution containing 1 mM EGTA the neurotransmitter releasing action of vinpocetine was abolished, however, its stimulating action on the resting [^{3}H]NA outflow was not changed. In Na-pump-inhibited arteries (K-free solution), where both the resting and the nerve stimulation-evoked release of neurotransmitter had already been increased, vinpocetine further enhanced the nerve stimulation-evoked release of [^{3}H]NA. It is concluded that vinpocetine may have α_2- and α_1-adrenoceptor blocking action, as well as a tyramine-like effect. The presynaptic neurotransmitter releasing action of vinpocetine is presumably the consequence of its inhibitory action on the Ca-pump which is suggested by the finding that in K-free solution vinpocetine was able to enhance further the release of neurotransmitter.

Vinpocetine (Cavinton) is widely used as a vasoregulator in cerebrovascular diseases (Kárpáti & Szporny 1976; Biró et al 1976; Miyazaki 1982; Otomo et al 1982, 1985; Imamoto et al 1984). In the present study we have investigated the pre- and post-synaptic action of vinpocetine at the peripheral sympathetic neuro-effector junction using the isolated main pulmonary artery of the rabbit. It was found that a high concentration of vinpocetine exerts a phentolamine-like as well as a tyramine-like action, i.e. it increases both the resting and the nerve stimulation-evoked release of [^{3}H]NA and inhibits the stimulation-evoked contraction of smooth muscle.

METHODS

Rabbit main pulmonary artery

The isolated main pulmonary artery of the rabbit (Starke et al 1974) was used. Rabbits of either sex (2–3 kg) were stunned by a blow on the neck. The main pulmonary artery was dissected and placed into Krebs solution which contained pargyline ($1{\cdot}2 \times 10^{-4}$ M) and was fully equilibrated with 5% CO_2, 95% O_2. The composition of the Krebs solution was (mM): Na^+, 137·4; K^+, 5·9; Ca^{2+}, 2·5; Mg^{2+}, 1·2; Cl^-, 122·1; $H_2PO_4^-$, 1·2; HCO_3^-, 25·0; SO_4^{2-}, 1·2; glucose, 11·5; ascorbic acid, 0·3; Na_2EDTA, 0·03. When K-free solution was used, KCl and KH_2PO_4 were omitted from the Krebs, and KCl (4·7 mM) was not substituted; however, KH_2PO_4 (1·2 mM) was substituted by an equimolar concentration of NaH_2PO_4. In Ca-free solution, $CaCl_2$ (2·5 mM) was omitted and 1 mM EGTA was added. Both K-free and Ca-free Krebs solutions were prepared using double-distilled water.

[^{3}H]Noradrenaline release measurement

The method was as described (Borowski et al 1977; Endo et al 1977; Török et al 1984a, b). Briefly, after the preparation had been placed in the Krebs solution, 25 µl of [^{3}H]NA was added to the incubation solution (final concn of [^{3}H]NA: $4{\cdot}2$–$4{\cdot}6 \times 10^{-7}$ M) for 45 min (pargyline was present). The temperature of the medium was 37 °C. Subsequently, the artery was suspended in an organ bath (capacity 2 ml) and superfused at a rate of 8 ml min^{-1} with 800 ml of medium containing the neuronal uptake blocker cocaine (3×10^{-5} M) instead of

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pargyline. At the end of the washing period the flow rate was changed to 4 ml min^{-1} and corticosterone (5×10^{-5} M) was also added to the Krebs solution to block the extraneuronal uptake of noradrenaline. In the present study the individual [^{3}H]compounds ([^{3}H]3,4-dihydroxyphenylglycol (DOPEG), [^{3}H]normethanephrine etc.) were not determined, however, Endo et al (1977) have found that, in the presence of cocaine and corticosterone, 86% of liberated NA is unmetabolized. On the basis of this assumption, and knowing the specific activity of [^{3}H]NA, the outflow of labelled neurotransmitter was calculated in pmol/3 min according to Endo et al (1977).

The perfusate was collected in 3 or 6 min samples. At the end of the experiments the preparations were dissolved in 1 ml Soluene (Packard) and the radioactivity of perfusate samples and tissues were determined by a liquid scintillation counter (Beckman, LS-9000). To release neurotransmitter, the artery was stimulated by electrical square-wave pulses (2 Hz, 1 ms, 60 V) for 3 min (360 pulses) using platinum wire electrodes. Tetrodotoxin (10^{-7} M) abolished the stimulation-evoked release of tritium, indicating the neuronal origin of the neurotransmitter release. The stimulation-evoked release of [^{3}H]NA was calculated by subtraction of the resting outflow immediately before stimulation from the release obtained during and up to 6 min after stimulation. Two control stimulation periods (S_1, S_2) were used and the drugs were added to the Krebs solution 18 min before the third stimulation period (S_3). The effect of the drugs was expressed as the ratio between the release of tritium ([^{3}H]NA in pmol) evoked by stimulation$_3$ and the overflow evoked by stimulation$_2$ (S_3/S_2). In control experiments the stimulation-evoked release ratio S_3/S_2 proved to be 0·95 ± 0·03 (mean ± s.e.) in seven identical experiments.

Stimulation technique

Square-wave pulses of 1 ms duration were delivered from a Grass S44 stimulator. The pulses were monitored on an oscilloscope. Two platinum wire electrodes were used for stimulation of nerves. The electrodes were fixed vertically on opposite sides of the tissue at the top and bottom of the organ bath. The distance between the tips of the electrodes was 20 mm.

Tension measurements

The same preparation was used for measuring the release of radioactivity and isometric tension. The pulmonary artery was mounted under 1 g tension and the stimulation-evoked contractions were measured with a 'strain-gauge' and recorded on a Servogor pen recorder.

Drugs, statistics

The following drugs were used: 1-[7-^{3}H]-noradrenaline, (sp. act. 35·9–40·0 Ci $mmol^{-1}$; Radiochemical Centre, Amersham, UK), pargyline hydrochloride (Serva), cocaine hydrochloride (Merck), corticosterone (Fluka), ascorbic acid (EGA), disodium ethylenediaminetetraacetate (Aldrich-Europe), tetrodotoxin (Calbiochem), (−)noradrenaline hydrochloride (Fluka), clonidine hydrochloride (Sigma), yohimbine hydrochloride (Koch-Light), prazosin hydrochloride (Pfizer), vinpocetine (Cavinton, Richter), ethyleneglycolbis(β-aminoethylether)*N,N'*-tetraacetic acid (EGTA, Serva). The drugs were dissolved in Krebs solution. Corticosterone was dissolved in propylene glycol (final concentration 0·05%). All of the chemicals used to prepare the Krebs solution were of analytical grade. Means ± s.e.m. are given. Significance of differences was calculated using the *t*-test; n = number of experiments.

RESULTS

Pre- and post-synaptic action of vinpocetine in normal external ionic environments

Vinpocetine in normal Krebs solution increased the nerve stimulation-evoked release of [^{3}H]NA. At low concentration, 3×10^{-7} M, vinpocetine was ineffective in influencing transmitter release (ratio: 1·00 ± 0·05; n = 5). This value did not differ from the control (ratio: 0·95 ± 0·03; n = 7; $P > 0·3$). With higher concentrations of vinpocetine, however, the nerve stimulation-evoked transmitter release significantly increased (Fig. 1). Vinpocetine 3×10^{-5} M, enhanced not only the nerve stimulation-evoked release of [^{3}H]NA (ratio 1·82 ± 0·10; n = 8; $P < 0·001$; Table 1), but also increased the resting outflow of labelled transmitter (from 0·20 ± 0·02 to 0·35 ± 0·04 pmol/3 min; $P < 0·02$) and inhibited the postsynaptic response to nerve stimulation by about 20–30% (Fig. 2). When the neuronal uptake blocker cocaine was not present, the resting transmitter outflow increasing action of vinpocetine was more pronounced (from 0·24 ± 0·03 to 0·61 ± 0·06 pmol/3 min; n = 4; $P < 0·01$). In Fig. 2 it also can be seen that after vinpocetine removal the pre- and postsynaptic events returned slowly to the original values. Exogenously applied (−)-NA (10^{-6} M)

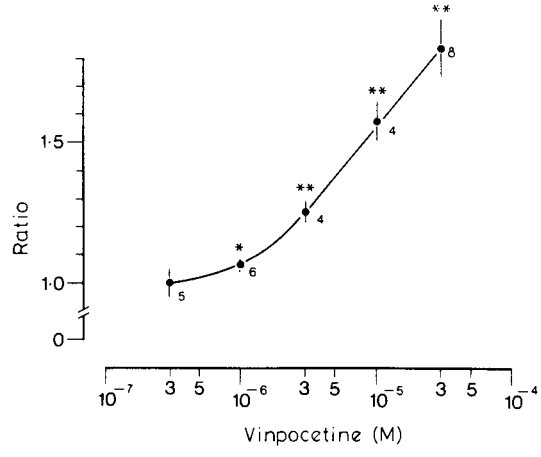

FIG. 1. Concentration-response relationship of vinpocetine-potentiated [^{3}H]noradrenaline release evoked by low frequency of nerve stimulation (2 Hz, 360 pulses). Ordinate: ratio between the overflow of [^{3}H] evoked by stimulation$_3$ and stimulation$_2$ (S_3/S_2); abscissa: log molar concentration of vinpocetine. Vinpocetine was perfused 18 min before stimulation$_3$. Means ± s.e.m. and the number of experiments are indicated. Significant differences from control: $*P < 0{\cdot}01$; $**P < 0{\cdot}001$. In control experiments the stimulation-evoked release ratio of S_3/S_2 was 0·95 ± 0·03 (n = 7).

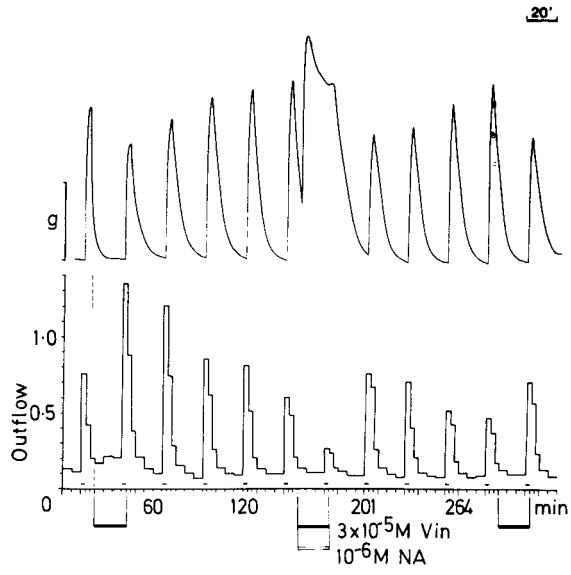

FIG. 2. Resting and nerve-evoked [^{3}H]NA releasing action of vinpocetine (3×10^{-5} M) and its inhibition by exogenously applied (−)-noradrenaline ((−)-NA, 10^{-6} M). Upper panel: isometric contraction of circular muscle. Lower panel: the outflow of [^{3}H]NA (pmol/3 min). Stimulation periods, indicated by filled horizontal bars above the axis, were applied at 27 min intervals. Vinpocetine increased both the resting and the nerve stimulation-evoked release of [^{3}H]NA and inhibited the postsynaptic contraction. (−)-NA inhibited the vinpocetine potentiated ^{3}H-release and increased the tone of smooth muscle. Note, that after vinpocetine removal the pre- and post-synaptic events returned slowly to the control values.

reversed the [^{3}H]NA release potentiating action of 3×10^{-5} M vinpocetine (ratio 0·36 ± 0·05; n = 3; $P < 0{\cdot}001$; Table 1) and contracted the smooth muscle as expected from the α_1-adrenoceptor-mediated depolarization (Fig. 2). The preferential α_2-adrenoceptor agonist, clonidine (10^{-6} M), was also effective in inhibiting the transmitter releasing action of vinpocetine (ratio 0·47 ± 0·06; n = 4). Clonidine by itself, 10^{-6} M, inhibited the nerve-evoked release of [^{3}H]NA (ratio 0·34 ± 0·08; n = 5) and increased the resting tone of smooth muscle by 1·16 ± 0·16 g (n = 5; not shown). This was abolished by the preferential α_1-adrenoceptor antagonist prazosin (10^{-7} M). When vinpocetine, 3×10^{-5} M, and clonidine, 10^{-6} M, were present together in the perfusing solution, increasing action of clonidine on the resting tone was significantly inhibited (0·58 ± 0·12 g; n = 4; $P < 0{\cdot}05$). The (−)-NA (10^{-6} M)-induced inhibition of vinpocetine (3 ± 10^{-5} M)-potentiated [^{3}H]NA release was partly antagonized by 3×10^{-7} M yohimbine, a preferential antagonist at presynaptic α_2-adrenoceptors (ratio 0·77 ± 0·21; n = 4; Fig. 3; Table 1), however the difference was not significant ($P > 0{\cdot}1$). Yohimbine (3×10^{-7} M) prevented the inhibitory action of vinpocetine on the postsynaptic contraction (Fig. 4) and did not enhance further the [^{3}H]NA release potentiated by vinpocetine (Table 1).

The action of vinpocetine in the absence of external calcium

In Ca-free, 1 mM EGTA-containing Krebs, where the external Ca should be reduced to about 10^{-9} M (Miledi & Thies 1971), vinpocetine (3×10^{-5} M) was ineffective in producing transmitter release (ratio 0·06 ± 0·02; n = 4; Fig. 5). Ca-removal by itself abolished both the nerve stimulation-evoked release of [^{3}H]NA (ratio −0·04 ± 0·05; n = 4) and the postsynaptic response (Fig. 5). On the other hand, Ca-removal did not affect the increasing action of vinpocetine on the resting transmitter outflow, i.e. in the absence of Ca and in the presence of vinpocetine the [^{3}H]NA outflow increased from 0·23 ± 0·01 to 0·36 ± 0·03 pmol/3 min (n = 4; $P < 0{\cdot}01$).

[^{3}H]Noradrenaline releasing action of vinpocetine in K-free solution

It is known that inhibition of the sodium-pump either by K-removal or application of ouabain increases the release of transmitter from the pulmonary artery

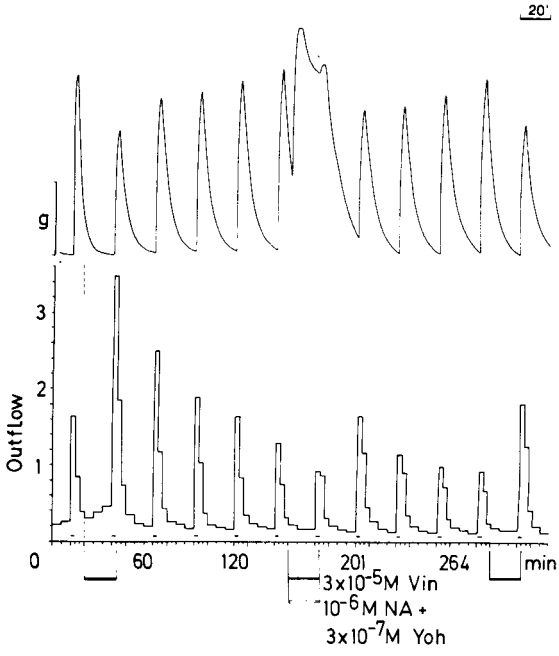

FIG. 3. Pre- and post-synaptic action of vinpocetine (3×10^{-5} M) in the absence and presence of 10^{-6} M (−)-NA + 3×10^{-7} M yohimbine. Upper panel: isometric contraction of smooth muscle. Lower panel: [^{3}H]NA outflow (pmol/3 min). Note, that yohimbine partly antagonized the (−)-NA evoked inhibition of vinpocetine-potentiated [^{3}H]NA release and did not affect the (−)-NA evoked postsynaptic contraction.

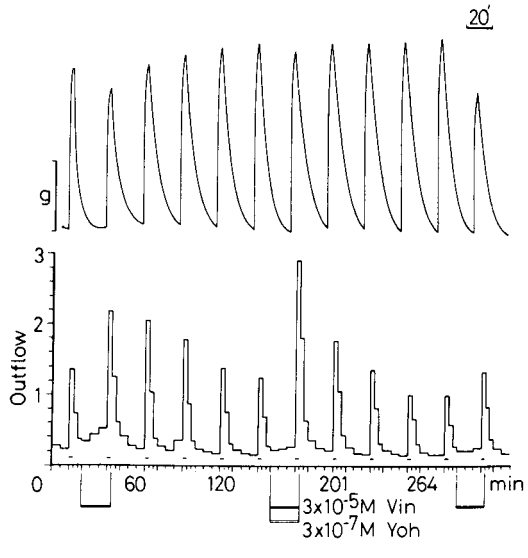

FIG. 4. Transmitter releasing action of vinpocetine (3×10^{-5} M) in the presence and absence of yohimbine (3×10^{-7} M). Upper panel: isometric contraction of smooth muscle. Lower panel: [^{3}H]NA outflow (pmol/3 min). Note that yohimbine further increased the vinpocetine-potentiated [^{3}H]NA release and antagonized the vinpocetine-evoked inhibition of contraction.

Table 1. [^{3}H]Noradrenaline releasing action of vinpocetine in the presence of cocaine (3×10^{-5} M) and corticosterone (5×10^{-5} M).

Treatment	Ratio of nerve stimulation*-evoked [^{3}H]NA release	Significance P
1. Control	0·95 ± 0·03 (7)	
2. Vinpocetine, 3×10^{-5} M	1·82 ± 0·10 (8)	2/1 < 0·001
3. (−)-NA, 10^{-6} M	0·14 ± 0·04 (8)	3/1 < 0·001 3/2 < 0·001
4. Yohimbine, 3×10^{-7} M	2·86 ± 0·19 (4)	4/1 < 0·001 4/2 < 0·001
5. (−)-NA, 10^{-6} M + yohimbine, 3×10^{-7} M	9·67 ± 0·20 (5)	5/1 > 0·1 5/2 < 0·001 5/3 < 0·001 5/4 < 0·001
6. Vinpocetine, 3×10^{-5} M + (−)-NA, 10^{-6} M	0·36 ± 0·05 (3)	6/1 < 0·001 6/2 < 0·001 6/3 < 0·01
7. Vinpocetine, 3×10^{-5} M + yohimbine, 3×10^{-7} M	2·78 ± 0·17 (8)	7/1 < 0·001 7/2 < 0·001 7/4 > 0·7
8. Vinpocetine, 3×10^{-5} M + (−)-NA, 10^{-6} M + yohimbine, 3×10^{-7} M	0·77 ± 0·21 (4)	8/1 > 0·2 8/2 < 0·001 8/5 > 0·7 8/6 > 0·1

* Stimulation parameters: 2 Hz, 1 ms, 60 V for 3 min (360 pulses). Ratio of nerve stimulation-evoked release was calculated as described by Endo et al (1977).

Drugs were added to the Krebs solution 18 min before stimulation$_3$ (S_3).

Means ± s.e.m. Number of experiments in brackets.

(Török et al 1984c; Vizi et al 1984) as in other preparations (Paton et al 1971; Vizi 1972, 1977; Baker & Crawford 1975; Nakazato et al 1978; Powis 1983; Török et al 1985). In K-free solution both the resting, and the nerve stimulation-evoked release of transmitter increased. After 45 min of K-removal the ratio of stimulation-evoked release of [^{3}H]NA was 4·59 ± 0·62 (n = 4; second stimulation in K-free solution). This value was further increased in the presence of 3×10^{-5} M vinpocetine (ratio 8·50 ± 0·29; n = 4). The difference was significant at a level of 0·01. On the other hand vinpocetine did not increase further the resting [^{3}H]NA outflow increasing action of K-removal (Δ pmol/3 min in the presence, 0·72 ± 0·23 (n = 4) and in the absence, 0·66 ± 0·27 (n = 4) of vinpocetine $P > 0·8$).

DISCUSSION

In the present study we have investigated the releasing action of vinpocetine on [^{3}H]NA in the isolated main pulmonary artery of the rabbit in the presence of uptake blockers. Vinpocetine (10^{-6} -3×10^{-5} M) potentiated the low frequency (2 Hz)

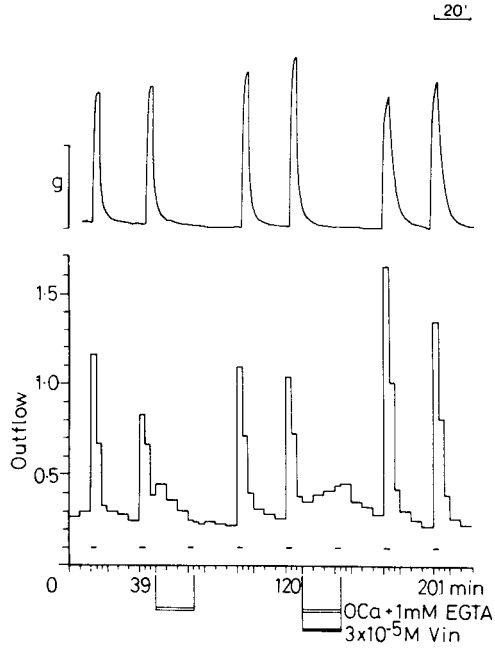

FIG. 5. The action of Ca-free (+ 1 mM EGTA) solution on nerve-evoked release of [^{3}H]NA and on postsynaptic response in the presence and absence of vinpocetine (3×10^{-5} M). Upper panel: isometric contractions. Lower panel: [^{3}H]NA outflow (pmol/3 min). Note that Ca-removal abolished the nerve-evoked pre- and post-synaptic events and that in Ca-free solution vinpocetine increased the resting output of [^{3}H]NA.

nerve stimulation-evoked [^{3}H]NA release and inhibited the postsynaptic response. These effects are similar to that of phentolamine, a well known α_1- and α_2-adrenoceptor blocker. The neurotransmitter-releasing action of vinpocetine was inhibited by activation of presynaptic α_2-adrenoceptors either by exogenously applied (−)-NA or clonidine. It has been suggested that exogenously applied agonists and antagonists do not compete for the same receptors, from the observation that yohimbine does not antagonize the inhibitory action of (−)-NA on transmitter release (Kalsner 1982; Baker et al 1984). This is not the case in the pulmonary artery of the rabbit, since 3×10^{-7} M yohimbine antagonized the inhibitory action of (−)-NA (3×10^{-7}, 10^{-6} M), and the extent of antagonism was dependent on the concentration of (−)-NA used. In the presence of 3×10^{-7} M (−)-NA and 3×10^{-7} M yohimbine, the ratio of nerve stimulation-evoked release was 1·62 ± 0·12 (n = 4). When a higher concentration of (−)-NA was used (10^{-6} M), this ratio decreased to 0·67 ± 0·20 (n = 5). It has been shown that α_2-receptors inhibit the voltage-dependent Ca-influx during the action potential (McAfee et al 1981; Starke 1981; Langer 1981). The preferential α_2-adrenoceptor blocking drug, yohimbine (Starke et al 1975; Vizi 1979) partly antagonized the (−)-NA-induced inhibition of [^{3}H]NA release by vinpocetine. On the other hand, vinpocetine did not further enhance the release of transmitter when the presynaptic α_2-adrenoceptor-mediated negative feedback mechanism was inhibited by yohimbine (Table 1). Furthermore the yohimbine-induced enhancement of transmitter release prevented the characteristic inhibitory action of vinpocetine on the postsynaptic contraction (Fig. 4). The α_1-adrenoceptor inhibitory action of vinpocetine was also supported by the finding that vinpocetine significantly inhibited the clonidine (10^{-6} M)-induced contraction of smooth muscle. In Ca-free, 1 mM EGTA-containing Krebs, where the external Ca-concentration should be reduced to about 10^{-9} M (Hubbard et al 1968; Miledi & Thies 1971), vinpocetine was ineffective in producing transmitter release. Ca-removal by itself abolished both the nerve stimulation-evoked release of [^{3}H]NA and the postsynaptic response, in agreement with the 'Ca-hypothesis' (Miledi 1973; Blaustein 1979; Baker & Knight 1984). On the other hand, Ca-removal did not inhibit vinpocetine's increasing action on the resting transmitter outflow. This suggests that vinpocetine also exerts a tyramine-like action. This was also shown by the finding that, in the absence of cocaine, vinpocetine further increased the resting outflow of labelled neurotransmitter. In Na-pump-inhibited nerve fibres (K-free solution) the release of [^{3}H]NA markedly increased. It is known that in response to Na-pump inhibition the influx of Ca increases resulting either from depolarization or activation of the reversed Na/Ca-exchange mechanism (Baker & Blaustein 1968; Baker et al 1969; Baker 1972; Blaustein 1974). In K-free solution vinpocetine significantly further enhanced the nerve-evoked release of [^{3}H]NA. This experimental finding raises the possibility that vinpocetine by its presynaptic transmitter releasing action exerts an inhibition of the nerve terminal Ca-pump (Schatzmann 1973), resulting in additional Ca-influx and transmitter release.

In conclusion, it seems that in peripheral sympathetic nerve fibres, vinpocetine exerts a phentolamine-like as well as a tyramine-like action. The vinpocetine-potentiated transmitter release may not cause vasoconstriction in the peripheral blood vessels, since vinpocetine inhibits the postsynaptic α_1-adrenoceptors as well.

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