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Transmitter releasing action of selegiline ((−)-deprenyl) from peripheral sympathetic nerves under different experimental conditions

TAMÁS L. TÖRÖK*, TÜNDE PAULÓ, PÉTER T. TÓTH, TINH THI NGUYEN, AWAD M. AZZIDANI AND KÁLMÁN MAGYAR

Department of Pharmacodynamics, Semmelweis University of Medicine, H-1089 Budapest, Nagyvárad-tér 4, P.O. Box: 370, Hungary

A high concentration of selegiline ((−)-deprenyl; 10^{-4} M) potentiated low frequency (2 Hz) nerve stimulation-evoked release of [^{3}H]noradrenaline from the isolated main pulmonary artery of the rabbit in the presence of neuronal (cocaine, 3×10^{-5} M) and extraneuronal (corticosterone, 5×10^{-5} M) uptake blockers, and inhibited the postsynaptic response. The transmitter-releasing action of 10^{-4} M selegiline was inhibited by a moderate increase of external K^+ (23·6 mM). Excess K^+ by itself abolished the nerve-evoked release of [^{3}H]noradrenaline but did not increase the resting outflow of radioactivity. Excess Ca^{2+} (7·5 mM) increased the stimulation-evoked transmitter release. In the presence of excess Ca^{2+}, selegiline (10^{-4} M) was effective in increasing the [^{3}H]noradrenaline release in response to nerve-stimulation. Excess Ca^{2+} partly antagonized the postsynaptic inhibitory action of selegiline. In Ca^{2+}-free, 1 mM EGTA-containing Krebs solution both the nerve-evoked ^{3}H release and the transmitter releasing action of selegiline were abolished, in agreement with the 'Ca-hypothesis'. The voltage-dependent K^+-channel blocker, 4-aminopyridine (10^{-5} M), increased the nerve-stimulation-evoked release of tritium from arteries. If selegiline was also present in the perfusion medium the nerve-evoked transmitter release further increased. 4-Aminopyridine completely antagonized the inhibitory action of selegiline on the postsynaptic contraction.

In a previous study it has been shown that high concentrations of selegiline ((−)-deprenyl) an inhibitor of the B form of monoamine oxidase enzyme discovered by Knoll & Magyar (1972), exerts an α_2- and α_1-adrenoceptor inhibitory action.

In the present study, we have investigated the α_2-adrenoceptor-mediated release by selegiline 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 under different experimental conditions which are known to modify the nerve-stimulation-evoked neurotransmitter release.

MATERIALS AND 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, opened longitudinally, fixed by two threads and placed in normal Krebs solution which contained pargyline ($1·2 \times 10^{-4}$ 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 excess K^+ (23·6 M, 4 times normal) solution was used, NaCl was replaced by an equimolar concentration of KCl. Excess Ca^{2+} (7·5 mM, 3 times normal) solution was prepared by simple addition of $CaCl_2$ to the Krebs solution without compensation. If Ca^{2+}-free solution was used, $CaCl_2$ was omitted and 1 mM ethyleneglycol-bis(β-aminoethylether) *N,N'*-tetraacetic acid (EGTA) was added. In the latter case double-distilled water was used for preparing the Krebs solution.

Measurement of [^{3}H]noradrenaline release

The method was essentially the same as described previously (Borowski et al 1977; Endo et al 1977; Török et al 1982, 1984a, 1985). Briefly, after the preparation had been placed in the Krebs solution, 25 μL of [^{3}H]noradrenaline ([^{3}H]NA) was added to the incubation solution (final concentration of [^{3}H]NA: $4·2–4·6 \times 10^{-7}$ 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) between platinum electrodes

* Correspondence and present address: Neuroscience Group, University of Newcastle, Faculty of Medicine, Newcastle, New South Wales, 2308 Australia.

fixed vertically on opposite sides of the tissue. The preparation was connected to a 'strain-gauge' transducer under 1 g tension and superfused with 800 mL solution containing cocaine (3×10^{-5} M) instead of pargyline. The flow rate of the solution was 8 mL min^{-1}. At the end of the washing period corticosterone (5×10^{-5} M) was also added to the medium for 30 min to block the extraneuronal uptake of NA and the flow rate was reduced to 4 mL min^{-1}. Tritiated metabolites of noradrenaline were not determined, however Endo et al (1977) have shown 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 release of labelled neurotransmitter was calculated in pmol/3 min according to the method of 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 was 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 both the stimulation-evoked release of tritium and the muscle-response, indicating the nervous origin of neurotransmitter release (Török & Magyar 1986; Magyar et al 1986). 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. There were seven stimulation periods in all experiments: after 142 (S_1), 169 (S_2), 196 (S_3), 223 (S_4), 250 (S_5), 277 (S_6) and 304 (S_7) min of perfusion. 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). Excess K^+ was added to the Krebs solution 18 min before S_3. Ca^{2+} was also added to, or removed from the solution 18 min before stimulation$_3$. The effect of 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 was 0·97 ± 0·01 (mean ± s.e.) in six identical experiments (Table 1).

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.

Table 1. [^{3}H]Noradrenaline releasing action of selegiline in the presence of cocaine (3×10^{-5} M) and corticosterone (5×10^{-5} M). Drugs were added to the Krebs solution 18 min before stimulation$_3$ (S_3). Ions were also added to, or removed from, the Krebs solution 18 min before S_3.

Treatment	Ratio of nerve stimulation*-evoked [^{3}H]NA release	Significance (P)
1. Control	0·97 ± 0·01 (6)	
2. Selegiline, 10^{-4} M	2·66 ± 0·06 (10)	2/1 < 0·001
3. 23·6 mM K^+	0·09 ± 0·04 (4)	3/1 < 0·001
4. 23·6 mM K^+ + selegiline, 10^{-4} M	0·08 ± 0·04 (4)	4/2 < 0·001 4/3 > 0·9
5. 7·5 mM Ca^{2+}	1·79 ± 0·06 (4)	5/1 < 0·001
6. 7·5 mM Ca^{2+} + selegiline, 10^{-4} M	3·64 ± 0·14 (4)	6/2 < 0·001 6/5 < 0·001
7. Ca^{2+}-free + 1 mM EGTA	−0·11 ± 0·04 (4)	7/1 < 0·001
8. Ca^{2+}-free + 1 mM EGTA + selegiline, 10^{-4} M	−0·09 ± 0·01 (4)	8/2 < 0·001 8/7 > 0·6
9. 4-Aminopyridine, 10^{-5} M	2·67 ± 0·18 (4)	9/1 < 0·001
10. 4-Aminopyridine, 10^{-5} M + selegiline, 10^{-4} M	4·70 ± 0·44 (4)	10/2 < 0·001 10/9 < 0·01

* 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).

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

Tension measurements

The same preparation was used for measuring the radioactivity and isometric tension. The pulmonary artery was opened longitudinally and 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), 4-aminopyridine (4-AP, Aldrich–Europe), selegiline ((−)-deprenyl, Chi-

noin), ethyleneglycol-bis(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 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

The inhibitory action of excess potassium on selegiline potentiated [³H]noradrenaline release

In normal external ionic environments selegiline, 10^{-4} M, significantly potentiated the nerve-stimulation-evoked [³H]NA release and inhibited the postsynaptic response (Fig. 1), as has been shown previously (Török et al 1984b). The ratio of nerve-evoked release of [³H]NA was 2·66 ± 0·06 ($n = 10$; $P < 0·001$; Table 1).

Lorenz & Vanhoutte (1975) have shown that a moderate increase of external K^+ (10–20 mM) inhibits the noradrenergic neurotransmission. Blaustein et al (1972) have found that K^+ up to 15–20 mM does not cause Ca^{2+} accumulation by synaptosomes and transmitter release. In the main pulmonary artery of the rabbit, excess K^+ (23.6 mM, 4 times of normal) did not affect the outflow of radioactivity but contracted the muscle (Fig. 1). On the other hand the nerve-evoked release of [³H]NA was abolished in 23·6 mM K^+-containing solution (ratio: 0·09 ± 0·04; n = 4; $P < 0·001$; Fig. 1). When selegiline (10^{-4} M) and excess K^+ were perfused together, the transmitter releasing action of selegiline was totally inhibited (ratio: 0·08 ± 0·04; $P < 0·001$; Fig. 1; Table 1).

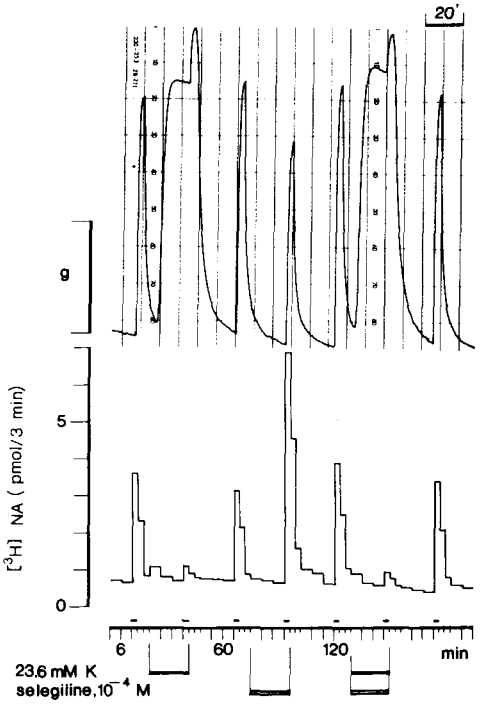

FIG. 1. Pre- and post-synaptic action of selegiline (10^{-4} M, □) in normal and excess K^+ (23·6 mM, ■) containing Krebs solution. Upper panel: isometric contraction of smooth muscle (g). Lower panel: the outflow of [³H]NA (pmol/3 min). Stimulation periods, indicated by filled horizontal bars above the axis, were applied at 27 min intervals. 23·6 mM K^+, which did not affect the resting outflow of [³H]NA, abolished the nerve-evoked release of ³H and increased the tone of smooth muscle. Selegiline by itself potentiated the nerve-evoked release of [³H]NA and inhibited the contraction. Excess K^+ completely antagonized the transmitter releasing action of selegiline.

[³H]Noradrenaline releasing action of selegiline in excess calcium containing solution

Kirpekar & Misu (1967) have shown that excess Ca^{2+} (7·5 mM) potentiates the release of NA from the perfused cat spleen in response to nerve stimulation. With a higher concentration of Ca^{2+} (20 mM) however, the NA release was decreased (Kirpekar et al 1972).

In our experiments excess Ca^{2+} (7·5 M, 3 times of normal) potentiated both the nerve-evoked release of [³H]NA and the postsynaptic response (Fig. 2). The stimulation-evoked release ratio proved to be 1·79 ± 0·06 (n = 4; $P < 0·001$). This value further increased if selegiline (10^{-4} M) was also present in the perfusion medium (ratio: 3·64 ± 0·14; n = 4; $P < 0·001$; Fig. 2; Table 1). From Fig. 2 it also can be seen that the selegiline induced inhibition of the postsynaptic response was partly antagonized by excess Ca^{2+}.

The lack of transmitter releasing action of selegiline in calcium-free solution

In Ca^{2+}-free, 1 mM EGTA containing solution, where the external Ca^{2+} concentration should be reduced to about 10^{-9} M (Hubbard et al 1968; Miledi & Thies 1971), the electrochemical gradient of Ca^{2+} presumably being reversed (Lev-Tov & Rahamimoff 1980), both the pre- and post-synaptic events were abolished in response to nerve-stimulation (Fig. 3). The ratio of nerve-evoked release of ³H was −0·11 ± 0·04 (n = 4; $P < 0·001$; Table 1). In Ca^{2+}-free solution selegiline (10^{-4} M) was ineffective in producing transmitter release (ratio: −0·09 ± 0·01; n =

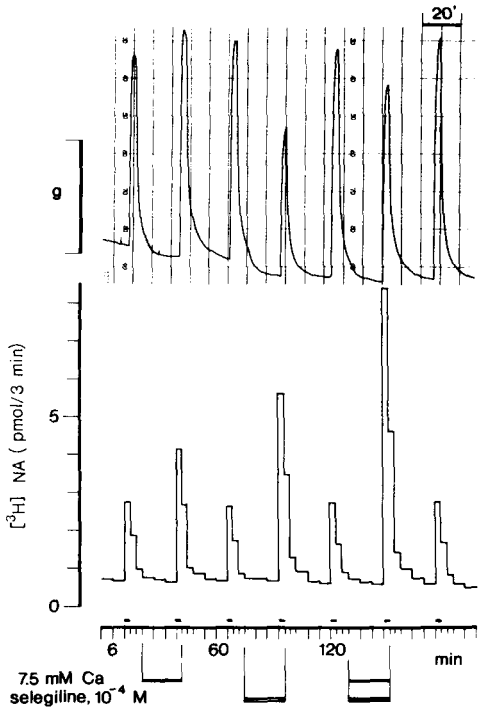

FIG. 2. The action of excess Ca^{2+} (7·5 mM, ■) on pre- and post-synaptic effect of selegiline (10^{-4} M, □). Upper panel: isometric contraction of smooth muscle (g). Lower panel: the outflow of [^{3}H]NA (pmol/3 min). Excess Ca^{2+} potentiated both the stimulation-evoked overflow of [^{3}H]NA and the contraction of smooth muscle. In the presence of 7·5 mM Ca^{2+}, selegiline further increased the transmitter release. Excess Ca^{2+} partly antagonized the contraction-inhibitory action of selegiline.

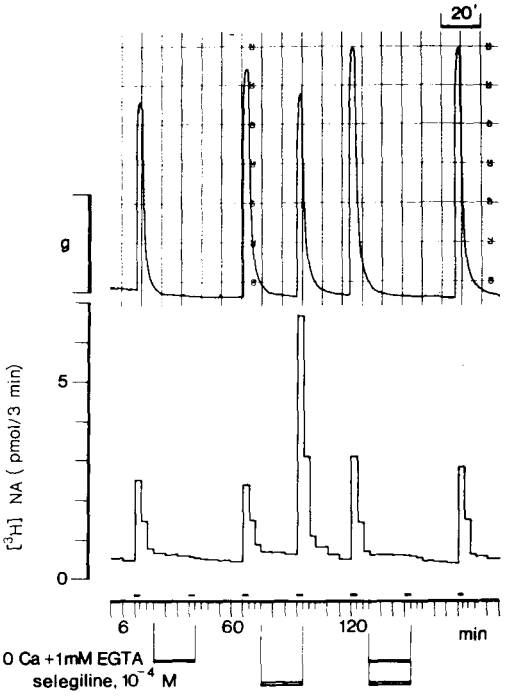

FIG. 3. The inhibitory action of Ca^{2+}-free solution (0 Ca + 1 mM EGTA, ■) on selegiline (10^{-4} M, □)-potentiated [^{3}H]NA release. Upper panel: isometric contraction of smooth muscle (g). Lower panel: the outflow of [^{3}H]NA (pmol/3 min). Ca^{2+} removal abolished both the [^{3}H]NA release and the postsynaptic response to nerve-stimulation. Selegiline was ineffective in producing transmitter release in the absence of external Ca^{2+}.

4; $P < 0.001$; Fig. 3), indicating the key role of Ca^{2+} in the presynaptic action of selegiline.

[^{3}H]Noradrenaline releasing action of selegiline in the presence of a potassium-channel blocker

It has been shown that 4-aminopyridine (4-AP) is a specific blocker of K^+-channels (Yeh et al 1976) and potentiates both cholinergic (Vizi et al 1977; Illés & Thesleff 1978) and noradrenergic (Johns et al 1976) transmission.

In our experiments, 10^{-5} M 4-AP significantly increased the release of [^{3}H]NA from the arteries (ratio: 2·67 ± 0·18; n = 4; $P < 0.001$; Fig. 4) and potentiated the postsynaptic response. When selegiline (10^{-4} M) was also present together with 4-AP in the perfusion solution, the release of [^{3}H]NA was further increased (ratio: 4·70 ± 0·44; n = 4; $P <$ 0·01; Table 1). Furthermore 4-AP was also effective in antagonizing the characteristic inhibitory action of selegiline on the postsynaptic contraction (Fig. 4).

DISCUSSION

In the present study we have investigated the [^{3}H]noradrenaline releasing action of the MAO-B inhibitor selegiline in the presence of uptake blockers. This drug is known to have a 'phentolamine-like' action (Török et al 1984b), i.e. it increases the release of [^{3}H]NA and inhibits the contraction of smooth muscle. In the previous study (Török et al 1984b), it was shown that the potentiating action of selegiline on NA release could be inhibited by exogenously applied (−)-NA, an action antagonized by the preferential α_2-adrenoceptor blocker, yohimbine. Furthermore, it was also found that selegiline is able to increase the [^{3}H]NA release further if it had already been increased by Na^+-pump inhibition (K^+-free perfusion).

Here the presynaptic α_2-adrenoceptor inhibitory action of a high concentration of selegiline (10^{-4} M) was investigated under different experimental conditions which are known to modify the transmitter's release from nerve terminals. In the main pulmonary

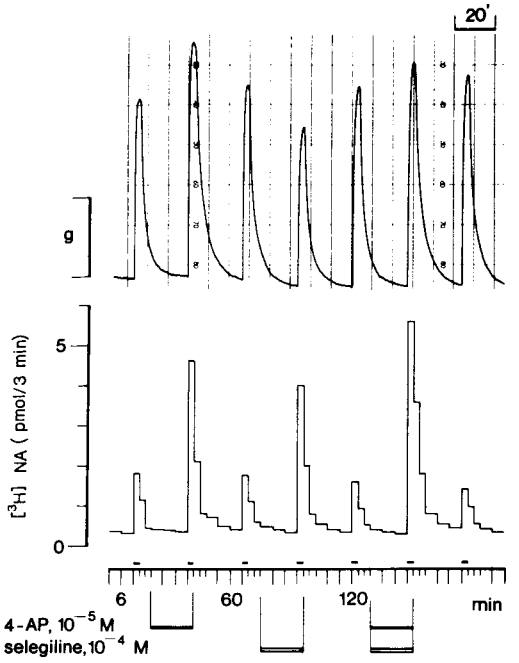

FIG. 4. The neurochemical transmission potentiating action of 4-aminopyridine (4-AP, 10^{-5} M, ■) in the presence and absence of selegiline (10^{-4} M, □). Upper panel: isometric contraction of smooth muscle (g). Lower panel: the outflow of [^{3}H]NA (pmol/3 min). 4-AP increased both the pre- and post-synaptic events during nerve-stimulation. In the presence of 4-AP, selegiline further increased the release of [^{3}H]NA. Note, that 4-AP antagonized the contraction-inhibitory action of selegiline.

artery of the rabbit a moderate increase of external K^+ (23·6 mM) did not increase the resting outflow of [^{3}H]NA. This finding is in good agreement with the observation of Blaustein et al (1972) who have shown that K^+ up to 15–20 mM does not cause accumulation of Ca^{2+} by synaptosomes or release of transmitter. On the other hand, both the nerve stimulation evoked release of [^{3}H]NA and the potentiating action of selegiline on transmitter release were abolished (Fig. 1). In agreement with these results, Lorenz & Vanhoutte (1975) have shown that excess K^+ (10–20 mM) inhibits [^{3}H]NA release from the dog isolated saphenous vein preparation in response to nerve stimulation. An elevated level of external K^+ is known to block action potential conductance (Grossman et al 1979; Smith 1980) due to inactivation of Na^+-channels (Hodgkin & Huxley 1952).

In contrast to these results, an increase of external Ca^{2+} (from 2·5 to 7·5 mM) potentiated the nerve-evoked release of [^{3}H]NA from the arteries (Table 1). This finding is consistent with the results of Kirpekar & Misu (1967) obtained on cat spleen. In nerve cells it is believed that electrical activity increases $[Ca^{2+}]_i$ by allowing an influx of Ca^{2+} through voltage-dependent Ca^{2+}-channels (Katz & Miledi 1969; Baker et al 1971; Baker 1972; Llinás & Hauser 1977; Blaustein 1979; Linás et al 1980). In the presence of excess Ca^{2+}, selegiline was effective in producing further transmitter release (Fig. 2). Since α_2-adrenoceptors are thought to inhibit the voltage-sensitive Ca^{2+}-influx in sympathetic neurons (McAfee et al 1981; Starke 1981), it is plausible to suppose that selegiline, an inhibitor of α_2-receptors, produces an additional activation of Ca^{2+}-channels and transmitter release. On the other hand, Ca^{2+}-removal from Krebs solution abolished the NA releasing action of selegiline (Fig. 3), indicating the key role of calcium in the α_2-adrenoceptor-mediated action of this compound.

It is known that in a Ca^{2+}-free solution containing 1 mM EGTA, in which the external Ca^{2+} concentration should be reduced to about 10^{-9} M (Hubbard et al 1968; Miledi & Thies 1971), the electrochemical gradient of Ca^{2+} is reversed (Lev-Tov & Rahamimoff 1980) and transmitter release subsequent to Ca^{2+}-entry cannot be triggered by electrical- or K^+-depolarization or through the Na^+/Ca^{2+}-exchange mechanism (Baker et al 1969; Landau 1969; Cooke et al 1973; Blaustein 1974; c.f. Baker & Crawford 1975). Ca^{2+} removal by itself abolished both the nerve-evoked release of transmitter (Table 1) and the postsynaptic response (Fig. 3), in agreement with the 'Ca-hypothesis' (Miledi 1973; Baker 1974; Blaustein 1979; Baker & Knight 1984).

The voltage-dependent K^+-channel blocker, 4-aminopyridine (Meves & Pichon 1975, 1977; Gillespie & Hutter 1975; Yeh et al 1976; Hermann & Gorman 1981), which in low concentration also partially inhibits the $(Ca^{2+})_i$- activated K^+-channels (Bartschat & Blaustein 1985), in a concentration of 10^{-5} M increased the stimulation-evoked [^{3}H]NA release from arteries, as in other preparations (Johns et al 1976; Vizi et al 1977; Illés & Thesleff 1978; Thesleff 1980), and as has been shown previously (Török et al 1984a). In the presence of 4-AP, selegiline was able to potentiate further the release of neurotransmitter (Fig. 4; Table 1). In addition, the characteristic α_1-adrenoceptor inhibitory action of selegiline was completely antagonized by 4-AP.

In conclusion it seems that the presynaptic α_2-adrenoceptor-mediated noradrenaline-releasing action of selegiline can be inhibited by (i) inactivation of Na^+-channels, and (ii) inhibition of voltage-

sensitive Ca^{2+}-channels. On the other hand, selegiline was effective in producing an additional transmitter release when (i) the Ca^{2+}-channels were activated and (ii) the voltage-dependent K^+-channels were blocked.

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