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Evidence for dopamine release and metabolism beyond the control of nerve impulses and dopamine receptors in rat substantia nigra

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In rat substantia nigra a biphasic disappearance curve of dopamine (DA) was seen after tyrosine hydroxylase inhibition by α-methyl-*p*-tyrosine (α-MT): the initial phase had a fast turnover and a half life of 0·5 h and the later phase had an extremely slow turnover. In contrast to the effects in striatum, neither haloperidol nor apomorphine influenced α-MT-induced DA disappearance in the substantia nigra. Furthermore, inhibition of impulse flow by γ-butyrolactone prevented DA disappearance in striatum but not in the substantia nigra. Measurements of DA and 3-methoxytyramine following treatment with inhibitors of monoamine oxidase (pargyline) and catechol-*O*-methyl transferase (tropolone) indicated that *O*-methylation is a more important metabolic pathway in the substantia nigra than in the striatum. The data are interpreted to indicate that the release and metabolism of DA in the substantia nigra are largely beyond the control of nerve impulses and DA receptors. It is suggested that such an arrangement forms an important feature of autoreceptor-mediated feedback control of DA nerve cell activity.

Using histochemical techniques, Björklund & Lindvall (1975) demonstrated the occurrence of dopamine (DA) not only in the cell bodies of the dopaminergic neurons in the substantia nigra (SN), but also in the dendritic network arising from these cells, and they suggested a role of DA as a transmitter in the SN. Some evidence for a release of DA in the SN has also been presented. Thus a calcium-dependent, potassium-evoked release of exogenously applied [^{3}H]DA from the rat SN has been demonstrated in-vitro (Geffen et al 1976; Silbergeld & Walters 1979). Furthermore, a potassium-evoked release of [^{3}H]DA, newly synthesized from [^{3}H]tyrosine, has been observed by a push and pull technique from cat SN in-vivo (Nieullon et al 1977).

The relationship between neuronal discharge and dendritic release of DA in the SN is, however, not clear. Electrical stimulation of nigrostriatal axons has been reported to cause increases in nigral 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) (Korf et al 1977). However, very high stimulation frequencies (30 Hz) and long duration (1 h) were used. Moreover, the increases in metabolite levels were much smaller in the SN than in the striatum. Thus the physiological significance of these observations is questionable. In-vivo release of DA in cat SN is not reduced by blocking fast sodium channels with tetrodotoxin (Nieullon et al 1977). However, in-vitro, veratridine, a drug known to depolarize nervous tissue by increasing the permeability to sodium ions, induces release of DA in rat SN and this effect is blocked by tetrodotoxin (Tâgerud & Cuello 1979).

In an effort to elucidate the regulation of nigral DA we have investigated the effects of various drugs, influencing the nigrostriatal DA neurons, mainly on DA disappearance after inhibition of tyrosine hydroxylase by α-methyl-*p*-tyrosine (α-MT). Striatal data are presented for comparison.

MATERIALS AND METHODS

Male, Sprague-Dawley rats (Anticimex, Stockholm, Sweden) (250–350 g) had free access to food and water and were kept under artificial lighting conditions (light between 0500 and 1900 h). The experimental procedures were all carried out during daytime.

Control rats received the same number of injections at corresponding times, vehicle replacing drugs. Injection volumes were 5 ml kg^{-1}. The following drugs were used: DL-α-methyl-*p*-tyrosine methylester HCl (H 44/68; Hässle, Mölndal, Sweden), pargyline HCl (Sigma, St Louis, USA), haloperidol (Janssen, Beerse, Belgium), apomorphine HCl (Apoteksbolaget, Göteborg, Sweden), γ-butyrolactone (GBL; Aldrich, Beerse, Belgium) and tropolone (Sigma, St Louis, USA). All compounds except haloperidol were dissolved in physiological (0·9%) saline (in the case of apomorphine, a

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few crystals of ascorbic acid were added to the solution to prevent oxidation). Haloperidol was dissolved in a minimal quantity of glacial acetic acid and made up to volume with 5·5% glucose solution.

The rats were decapitated and the brains were quickly removed and placed on an ice-cold glass plate. The corpora striata were dissected free (Carlsson & Lindqvist 1973) and the mesencephalon was divided into two parts with a cut from the ventral side perpendicular to the long axis of mesencephalon exactly at the caudal border of median eminence. The two SNs could then easily be identified and dissected free. The ventral tegmental area (A 10) was not included. The two SNs from one rat were pooled and the average weight of the nigral tissue was 5 mg. The time for one dissection never exceeded 8 min. After dissection the brain parts were immediately frozen on dry ice and stored at −70 °C. Biochemical analyses were performed by means of HPLC with electrochemical detection (LCEC). Frozen tissue was homogenized with 0·1 M $HClO_4$ containing 4·3 mM Na_2-EDTA and 4·2 mM $Na_2S_2O_5$. After centrifugation (10 000*g*, 0 °C for 10 min) 0·5 ml of the supernatant was taken for analysis of 3-methoxytyramine (3-MT). For the analysis of dopamine (DA), 20 mg of acid-washed Al_2O_3 was added to 1 ml supernatant (Felice et al 1978). The LCEC system consisted of a LDC-minipump (Laboratory Data Control), a stainless steel column (0·45 × 15 cm) packed with Nucleosil, RP-18, 5 μm (Macherey-Nagel). The detection was carried out electrochemically by means of a thin layer cell, TL-3 (Bioanalytical Systems) with a carbon paste working electrode, an Ag/AgCl reference electrode and an amperometric detector. The detector was operated at +0·65 V (DA) or +0·85 V (3-MT). The current produced was monitored using a linear recorder (Omniscribe, Houston Instruments). DA was chromatographed using a mobile phase consisting of 0·015 M K_2HPO_4, 0·035 M citric acid (pH 2·7–2·9), 0·26 mM Na-octyl-sulphate, 0·054 mM Na_2-EDTA and 8–10% v/v methanol. The mobile phase in the analysis of 3-MT was composed of 0·05 M citrate buffer (pH 4·0) containing 0·20 mM Na-octyl-sulphate, 0·054 mM Na_2-EDTA and 8–12% v/v methanol. The flow rate was 1·5–2 ml min^{-1} in both systems. As internal standards, α-methyl-DOPA and *N*-methyl-5-hydroxytryptamine were used for DA and 3-MT, respectively.

Protein concentration of the SN tissue samples was determined by analysing 100 μl of homogenate according to a modification of the Lowry procedure (Lowry et al 1951; Markwell et al 1978).

*α-Methyl-*p*-tyrosine (α-MT)-induced disappearance of dopamine in substantia nigra and striatum*

Time course. The concentration of dopamine was determined at various times (0·5–2 h) after an i.p. injection of α-MT (250 mg kg^{-1}).

Effects of haloperidol and apomorphine. In one experiment, haloperidol (0·25 mg kg^{-1} i.p.) or apomorphine (0·1 mg kg^{-1} + 0·1 mg kg^{-1}, s.c.) together with α-MT (250 mg kg^{-1} i.p.) were given 1 h before the rats were killed. The second dose of apomorphine was given 30 min before death. In a second experiment, haloperidol (2 mg kg^{-1} i.p.) or apomorphine (2 mg kg^{-1} + 2 mg kg^{-1} s.c.) together with α-MT (250 mg kg^{-1} i.p.) were given 2 h before the rats were killed. The second dose of apomorphine was given 1 h before death.

Effects of γ-butyrolactone (GBL), pargyline and tropolone. GBL (750 mg kg^{-1} + 250 mg kg^{-1} i.p.), pargyline (75 mg kg^{-1} i.p.) and/or tropolone (100 mg kg^{-1} + 50 mg kg^{-1} i.p.) were given together with α-MT (250 mg kg^{-1} i.p.) 2 h before the rats were killed. The additional doses of GBL and tropolone were given 1 h before death.

Effects of pargyline and tropolone on 3-MT levels

To check the completeness of tropolone-induced catechol-*O*-methyl transferase (COMT) inhibition in-vivo, we investigated if tropolone (100 mg kg^{-1} + 50 mg kg^{-1} i.p.) could inhibit pargyline (75 mg kg^{-1} i.p.)-induced 3-MT accumulation. The drugs were injected 2 h before the rats were killed. The second dose of tropolone was given 1 h before death.

Effects of pargyline on dopamine and 3-MT levels

To get further insight into the relative importance of *O*-methylation in SN and striatum we measured DA and 3-MT in the two areas 2 h after pargyline (75 mg kg^{-1} i.p.) or vehicle.

Statistical analysis

For statistical evaluation, analysis of variance followed by Student's *t*-test, or Mann-Whitney U-test were used.

RESULTS

α-MT-induced disappearance of dopamine in substantia nigra and striatum

Time course. The disappearance curve of DA after synthesis inhibition by α-MT is different in SN compared with striatum (Fig. 1). In striatum there is a gradual and continuous decline of DA after α-MT,

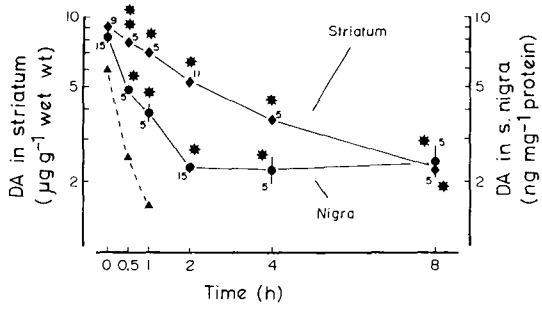

FIG. 1. Dopamine concentration in substantia nigra and striatum at various times after an injection of α-methyl-*p*-tyrosine (250 mg kg^{-1} i.p.). Shown are the means ± s.e.m. Statistics: analysis of variance followed by *t*-test; $*P < 0{\cdot}001$, $**P < 0{\cdot}01$ v.s. control. ○ Striatum, ● substantia nigra, △ substantia nigra after subtraction of the dopamine value of the plateau phase, i.e. 2, 3 ng (mg protein)$^{-1}$.

but in SN there seems to be a fast decline during the first 2 h and then DA levels remain essentially unchanged for at least 6 h. The half life of DA in striatum was estimated to be 2·6 h. Assuming that DA in SN is located in two different functional pools, one with a high and the other with a low turnover rate, the half life of DA in the high turnover rate pool would be 0·5 h (see the dashed curve in Fig. 1). The turnover of DA was calculated to be 16 nmol (g wet weight)$^{-1}$ h^{-1} in striatum and 7·2 nmol (g wet weight)$^{-1}$ h^{-1} or 52 nmol (g protein)$^{-1}$ h^{-1} (based on analyses showing that in SN, 14% of the wet weight is protein.

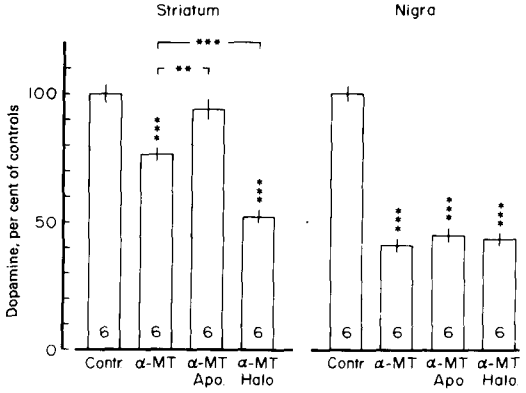

FIG. 2. The effect of apomorphine (Apo, 0·1 mg kg^{-1} + 0·1 mg kg^{-1} s.c.) and haloperidol (Halo, 0·25 mg kg^{-1} i.p.) on the α-methyl-*p*-tyrosine (α-MT, 250 mg kg^{-1} i.p.)-induced disappearance of dopamine in striatum and substantia nigra. All drugs were injected 1 h before the rats were killed. The second dose of apomorphine was given 30 min before death. Shown are the means ± s.e.m. for the number of rats indicated in the columns. Percentages were calculated on the basis of the control values. Pooled dopamine controls were 11·07 ± 0·38 μg (g wet weight)$^{-1}$ in striatum and 8·79 ± 0·27 ng mg protein^{-1} in substantia nigra. Statistics: analysis of variance followed by *t*-test; $***P < 0{\cdot}001$, $**P < 0{\cdot}01$.

Effects of haloperidol and apomorphine. One hour after the injection of α-MT, DA had decreased to 75% in striatum and to 40% in SN. When haloperidol (0·25 mg kg^{-1}) or apomorphine (0·1 mg kg^{-1} × 2) was given together with α-MT, a great discrepancy between the two regions could be seen. In striatum, haloperidol enhanced and apomorphine retarded α-MT-induced DA disappearance. In contrast, neither haloperidol nor apomorphine influenced the disappearance of DA in SN (Fig. 2). The same results were obtained when α-MT was given 2 h before death combined with higher doses of haloperidol (2 mg kg^{-1}) and apomorphine (2 mg kg^{-1} × 2) (Fig. 3).

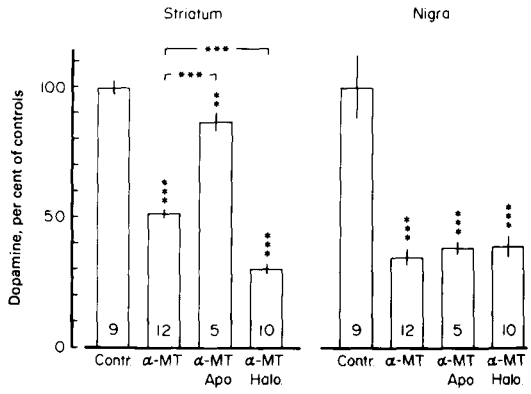

FIG. 3. The effect of apomorphine (Apo, 2 mg kg^{-1} + 2 mg kg^{-1} s.c.) and haloperidol (Halo, 2 mg kg^{-1} i.p.) on the α-methyl-*p*-tyrosine (α-MT, 250 mg kg^{-1} i.p.)-induced disappearance of dopamine in striatum and substantia nigra. All drugs were injected 2 h before the rats were killed. The second dose of apomorphine was given 1 h before death. Shown are the means ± s.e.m. for the number of rats indicated in the columns. Percentages were calculated on the basis of the control values. Pooled dopamine controls were 8·88 ± 0·24 μg (g wet weight)$^{-1}$ in striatum and 3·68 ± 0·44 ng (mg protein)$^{-1}$ in substantia nigra. Statistics: analysis of variance followed by *t*-test; $***P < 0{\cdot}001$, $**P < 0{\cdot}01$.

Effects of GBL, pargyline and tropolone. Inhibition of impulse flow by GBL totally prevented DA disappearance in striatum but had no effect in SN (Fig. 4). In SN, tropolone and pargyline in combination with GBL partially, but significantly, prevented the α-MT-induced disappearance of DA.

Pargyline, tropolone and GBL in combination had the same effect in striatum as GBL alone on α-MT-induced disappearance of DA. Tropolone

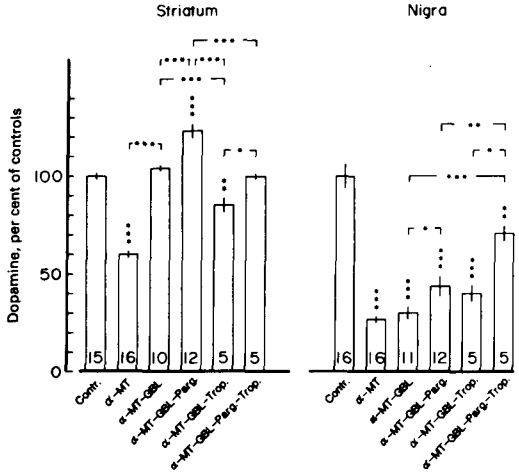

FIG. 4. The effect of γ-butyrolactone (GBL, 750 mg kg^{-1} + 250 mg kg^{-1}), pargyline (Parg, 75 mg kg^{-1}) and tropolone (Trop, 100 mg kg^{-1} + 50 mg kg^{-1}) on the α-methyl-*p*-tyrosine (α-MT, 250 mg kg^{-1} i.p.)-induced disappearance of dopamine in striatum and substantia nigra. All drugs were injected i.p. 2 h before the rats were killed. The additional doses of GBL and tropolone were given 1 h before death. Shown are the means ± s.e.m. for the number of rats indicated in the columns. Percentages were calculated on the basis of the control values. Pooled dopamine controls were 9·05 ± 0·16 μg (g wet weight)$^{-1}$ in striatum and 9·04 ± 0·54 ng (mg protein)$^{-1}$ in substantia nigra. Statistics: analysis of variance followed by *t*-test; $^{***}P < 0{\cdot}001$, $^{**}P < 0{\cdot}01$, $^{*}P < 0{\cdot}05$.

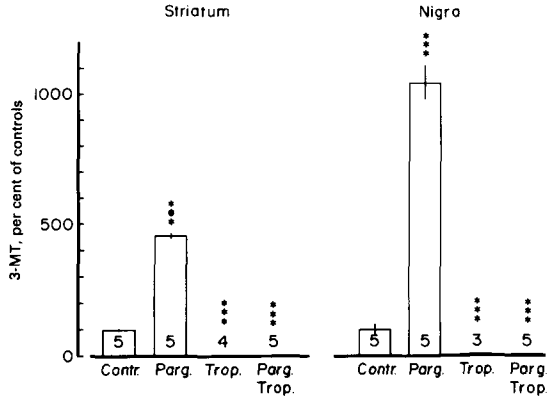

FIG. 5. The effect of pargyline (Parg, 75 mg kg^{-1} i.p.) and tropolone (Trop, 100 mg kg^{-1} + 50 mg kg^{-1} i.p.) on 3-methoxytyramine (3-MT) levels in striatum and substantia nigra. The drugs were injected 2 h before the rats were killed. The second dose of tropolone was given 1 h before death. Shown are the means ± s.e.m. for the number of rats indicated in the columns. Percentages were calculated on the basis of the control values. Pooled 3-MT controls were 0·32 ± 2 μg (g wet weight)$^{-1}$ in striatum and 0·77 ± 0·14 ng (mg protein)$^{-1}$ in substantia nigra. Statistics: analysis of variance followed by *t*-test; $^{***}P < 0{\cdot}001$.

together with GBL significantly enhanced α-MT-induced DA disappearance compared to GBL alone in striatum. Pargyline in combination with GBL and α-MT, unexpectedly increased DA levels above control levels in striatum.

Effects of pargyline and tropolone on 3-MT levels

Both in SN and striatum, tropolone could totally prevent the pargyline-induced 3-MT increase (Fig. 5).

Effect of pargyline on dopamine and 3-MT levels

As shown in Table 1, *O*-methylation appears to be a more important pathway in SN than in striatum, the molar 3-MT/DA ratio after pargyline treatment being 0·5 and 0·1, respectively.

Table 1. Effect of pargyline (75 mg kg^{-1} i.p. 2 h before death) on dopamine (DA) and 3-methoxytyramine (3-MT) levels in striatum and substantia nigra (SN). Shown are means ± s.e.m. 3-MT/DA ratios given are means of individual ratios. Statistics: Mann-Whitney U-test.

	Controls		Pargyline	
	Striatum (n = 5) nmol (g tissue)$^{-1}$	(n = 4) SN pmol (mg protein)$^{-1}$	Striatum (n = 5) nmol (g tissue)$^{-1}$	(n = 5) SN pmol (mg protein)$^{-1}$
DA	69·000±2·3	80·000±3·5	85·00±0·7	96·00±8·6
3-MT	1·890±0·046	3·000±0·10	8·60±0·25	48·00±3·2
3-MT/DA	0·027±0·001	0·035±0·013	0·10±0·003	0·51±0·024*

* Substantia nigra vs striatum, $P = 0{\cdot}008$.

DISCUSSION

The half-life and turnover of DA in striatum observed in this study are in agreement with previous measurements using α-MT-induced disappearance (Brodie et al 1966; Doteuchi et al 1974). In SN we found one initial phase with a fast turnover and a half-life of 0·5 h, i.e. about 5 times shorter than in striatum, followed by a phase with extremely slow turnover. The nature of the phase with slow turnover is obscure.

In agreement with previous observations (Andén et al 1967, 1971), haloperidol was found to enhance and apomorphine to retard the α-MT-induced disappearance of DA in striatum, probably due to receptor-mediated alterations in impulse flow and transmitter release. In contrast, neither of these agents influenced the disappearance of DA in SN. Confirming previous observations (Walters et al 1973), GBL, which has been shown to inhibit firing of DA cells in SN (Roth et al 1974), totally prevented DA disappearance in striatum; however it had no effect on DA disappearance in SN. Thus, in SN, in contrast to striatum, α-MT-induced disappearance

of DA seems to be independent of neuronal firing as well as of DA receptor activity. These observations are in accord with those of Westerink (1979), who found that the pargyline-induced accumulation of 3-methoxytyramine (3-MT) was essentially not influenced by γ-hydroxybutyric acid, haloperidol and apomorphine in SN but exerted the expected effects in striatum.

In this context DA release in SN, studied in cats by means of push and pull technique, often appears to vary in the opposite direction to striatal DA release (Cheramy et al 1981); that the latter release is indeed mediated by nerve impulses is supported by experiments in rats, using a dialysis technique (Imperato & Di Chiara 1984).

The present investigation provides evidence in favour of the view that 3-*O*-methylation is a relatively important pathway in the SN. Thus, in GBL-treated rats inhibition of COMT by tropolone tended to retard the α-MT-induced disappearance of DA in SN, whereas the opposite effect was observed in striatum. Moreover, when inhibition of COMT by tropolone in the same model was superimposed upon inhibition of MAO by pargyline, a clearcut retardation of DA disappearance was found in SN, in contrast to the enhancement in striatum. Further support for a relatively prominent role of COMT in nigral DA metabolism was provided by experiments where pargyline had been given 2 h before death: the percentage accumulation of 3-MT in SN was clearly more marked than in striatum, whereas the percentage accumulation of DA was roughly the same in the two regions. The difference between the two regions is well illustrated by the molar 3-MT/DA ratios 2 h after pargyline: 0·1 in striatum, 0·5 in SN. The evidence for *O*-methylation as an important metabolic pathway in SN is of particular interest in view of the fact that COMT is probably not located within the dopaminergic neuron: *O*-methylation is thus presumably preceded by release and appears, in fact, to be a useful indicator of release into the extraneuronal space (Carlsson & Hillarp 1962; Jonason & Rutledge 1968; Kehr 1976).

The most reasonable interpretation of the available data is that not only the metabolism but also the release of DA in SN is independent of firing and DA-receptor activity. Such an arrangement might well form an important feature of the autoreceptor-mediated feedback control of dopaminergic neurons: it will obviously raise the power of this feedback, when compared with a situation where the release is mediated by the nerve impulses and controlled by DA-receptor activity. In the latter case the feedback regulation will be limited by the fact that the release process itself is included in the feedback control. A firing- and receptor-independent release process should be primarily determined by the intraneuronal concentration of free and unbound DA. The high turnover rate of a nigral DA pool will lead to rapid changes in this concentration following variations in precursor availability or in the activity of e.g. tyrosine hydroxylase or monoamine oxidase. The resultant changes in release and autoreceptor activation would imply a strong and relatively unquenched feedback control of the firing rate of DA neurons.

Against the interpretation presented above it may be argued that a calcium-dependent, potassium-evoked release of DA in SN has been reported (see Introduction). However, the question may be raised whether observations on potassium-evoked release permit extrapolation to nerve impulse-mediated release. Llinas et al (1984) have proposed a possible mechanism for dendritic release of DA in SN, based on Ca^{2+} conductances. Possibilities for a specific control of dendritic DA release would thus appear to exist.

Although nigral DA metabolism was strongly inhibited by combined treatment with inhibitors of MAO and COMT, some disappearance of DA still took place under such conditions. This was probably not due to incomplete inhibition of the two enzymes. Certainly tropolone in the dosage employed appeared to block COMT completely, as judged by the prevention of 3-MT formation. The available evidence likewise indicates that pargyline, 75 mg kg^{-1} i.p., induces a rapid and virtually complete inhibition of MAO (see e.g. Wilk et al 1975). Among additional metabolic pathways conjugation may be considered. In a striatal perfusate preparation, 15% of the released DA was found to be sulphate conjugated (Tyce & Rorie 1982). To our knowledge no data on DA conjugation in rat SN are available. Removal of DA by axonal transport is an alternative possibility, but again no data are available to elucidate the possible role of this mechanism.

In striatum, DA levels were found to increase following combined treatment with α-MT, pargyline and GBL, suggesting that the inhibition of tyrosine hydroxylase was incomplete, at least initially. Another paradoxical observation was the decrease in striatal DA levels, when tropolone was superimposed upon α-MT, pargyline and GBL. Hypothetically, this could be explained by assuming that tropolone, which has been shown to be capable of inhibiting tyrosine hydroxylase (Broch 1972), made

the α-MT-induced inhibition of this enzyme more complete.

In conclusion, our data indicate that in SN, in contrast to striatum, the release and metabolism of DA is independent of firing and DA-receptor activity. We propose that this arrangement serves to strengthen the autoreceptor-mediated feedback regulation of dopaminergic nerve-cell activity.

Acknowledgements

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