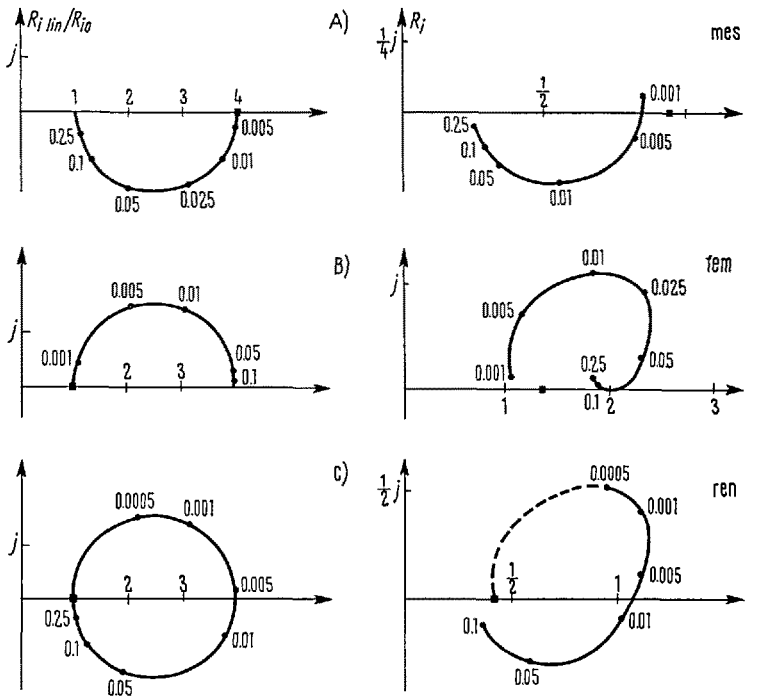

Fig. 2. Left column: Calculated Nyquist diagrams of the normalized input impedance according to equation 2. A) Pure autoregulation of flow, $G_p = 0$, $G_q = 3/(1 + j\omega\, 5)$, where $j = (-1)^{1/2}$ and ω: circular frequency (rad. sec^{-1}). B) Autoregulation of pressure, $G_p = 3/(1 + j\omega\, 100)$. A constant gain factor $G_q = 3$ was assumed for proper scaling of the diagram. C) Autoregulation of pressure and flow. $G_q = 3/(1 + j\omega\, 5)$ and $G_p = 3/(1 + j\omega\, 10^3)$. Right column: Measured Nyquist diagrams of the input impedance of the mesenteric artery (MES, units mm Hg/ml/min), femoral artery (FEM, units mm Hg/ml/min) and renal artery (REN, units mm Hg/ml/100 g/min). Average dog weight 20 kg. Flow was used as modulated input signal with the modulated amplitude being about 40% of the mean flow value. Parameters frequency in Hz. Squares: Zero frequency resistance as measured during constant perfusion with mean flow value.

pump from a cannula inserted in one femoral artery. The pump rate could be modulated. Using a TR-48 analog computer in the control circuit both, the arterial perfusion flow or local arterial pressure could be modulated sinusoidally in the frequency range between 0.0005 Hz and 0.25 Hz according to signals from a function generator. The responses of pressure and flow, respectively, were recorded. Each arterial bed was examined in at least 3 different animals. The responses were reasonably linear in the examined range.

The right column of Figure 2 shows characteristic results from the A. mesenterica sup. (MES), the A. femoralis (FEM) and the A. renalis (REN) in the form of Nyquist diagrams of the input impedance. The left column of Figure 2 shows Nyquist diagrams calculated according to equation 2 for the following assumptions: A) pure autoregulation of flow; B) autoregulation of pressure and C) reciprocal autoregulation of pressure and flow. First order transfer functions were assumed for G_q and G_p, as indicated in the figure.

From these results it can be concluded that there exists an autoregulation of pressure besides the wellknown autoregulation of flow[3] in all 3 examined beds. Although the experimental results certainly are distorted by nonlinear effects, it can be seen that the effect of the autoregulation of pressure is most marked in the femoral artery, whereas the mesenteric artery exhibits nearly pure autoregulation of flow. The renal artery shows both autoregulation of flow and pressure. The time constant of the latter is in the order of 1000 sec.

The existence of an autoregulation of pressure indicates that local control mechanisms take part in the dynamic regulation of the arterial pressure and may do so even in the absence of neural control[4].

Zusammenfassung. Der Eingangswiderstand verschiedener Arterien wurde im Niederfrequenzbereich (0,0005 bis 0,25 Hz) mittels sinusförmig modulierter Pumpen-Perfusion mit arteriellem Blut an narkotisierten Hunden gemessen. Die Resultate lassen die Existenz zweier reziprok wirkender Autoregulationsmechanismen vermuten, deren Frequenzcharakteristik mit Hilfe eines einfachen linearen Modells simuliert werden konnte.

TH. KENNER and K. ONO

Division of Biomedical Engineering,
University of Virginia, Medical Center, Box 224,
Charlottesville (Virginia 22901, USA),
18 January 1971.

[3] P. C. JOHNSON, Circulation Res. *15*, Suppl. 1 (1964).
[4] Supported by NIH Grant No. HE 11747.

Effects of L-Dopa Alone and in Combination with Dopa Decarboxylase Inhibitors on the Arterial Pressure and Heart Rate of Dogs

L-3,4-Dihydroxyphenylalanine (L-dopa) is known to produce clinical improvement in patients with Parkinson's disease[1]. Side effects of L-dopa given orally include hypotension[1–3], while by i.v. administration L-dopa elevates arterial pressure in man[4]. In experimental animals the acute effect of L-dopa on the arterial pressure is species dependent. By i.v. administration L-dopa elevates arterial pressure in cats[5] but lowers it in rabbits[6].

The possible mechanisms of the hypotensive action of L-dopa include: 1. replacement of norepinephrine at the peripheral sympathetic nerve endings with dopamine, which is a weaker α-adrenergic stimulant than norepine-

Table I. Effect of L-dopa alone and in combination with dopa-decarboxylase inhibitors on the arterial pressure of anesthetized dogs

Group No.	Treatment	Dose (mg/kg i.v.)	No. of animals	Mean arterial pressure (mm Hg)[a]						
				Control values	At min after drug					
					1	5	15	30	60	120
1	Control (acidic saline)		5	155	157	158	154	155	154	143
2	L-dopa	10	7	115	111	121	126	117	115	119
3	L-dopa	25	5	148	131	166	196[b]	150	158	160
4	L-dopa	50	5	132	125	198[b]	207[b]	182	120	102
5	L-HMD	15	4	127	127	127	127	125	125	127
6	L-HMD + L-dopa	15 + 25	7	145	135	126	85[b]	85[b]	96[b]	109[b]
7	L-HMD + L-dopa	15 + 50	5	109	99	81	72[b]	69[b]	67[b]	76[b]
8	Ro 4-4602	100	5	145	142	158	150	140	138	138
9	Ro 4-4602 + L-dopa	100 + 25	7	164	156	157	145	142[b]	137[b]	134[b]

[a] Average values for the given number of animals. [b] Significantly different from control value for the same group; $p < 0.05$.

Table II. Effect of L-dopa alone and in combination with dopa-decarboxylase inhibitors on the heart rate of anesthetized dogs

Group No.	Treatment	Dose (mg/kg i.v.)	No. of animals	Heart rate, beats/min[a]						
				Control values	At min after drug					
					1	5	15	30	60	120
1	Controls (acidic saline)		5	149	150	151	151	143	131	117
2	L-dopa	10	7	154	153	168	178	170	151	140
3	L-dopa	25	5	144	151	140	101[b]	184[b]	170	141
4	L-dopa	50	5	158	153	122	81[b]	129	193	168
5	L-HMD	15	4	159	151	147	149	133[b]	136	126[b]
6	L-HMD + L-dopa	15 + 25	7	154	152	150	112[b]	104[b]	106[b]	110[b]
7	L-HMD + L-dopa	15 + 50	5	150	153	142	106	105[b]	98[b]	87[b]
8	Ro 4-4602	100	5	159	158	162	164	158	145	123[b]
9	Ro 4-4602 + L-dopa	100 + 25	7	138	140	138	136	142	138	128

[a] Average values. [b] Significantly different from control value for the same group; $p < 0.05$.

phrine and may, therefore, function as a false transmitter, or 2. a central mechanism involving stimulation of inhibitory dopaminergic or adrenergic receptors in the central nervous system. Both hypotheses assume that L-dopa is pharmacologically inert and that one of its metabolites, probably dopamine or norepinephrine, is responsible for its hypotensive activity. Evidence of the existence of an enzymatic barrier (dopa-decarboxylase) between blood and brain for L-dopa[7,8] further indicates a metabolite but not L-dopa itself induces hypotension centrally.

The first hypothesis is supported by observations of COLLINS and WEST[9] that L-dopa can cause accumulation of dopamine in the sympathetic nerve terminals and that dopamine can be released by nerve stimulation. The second hypothesis is strengthened by recent findings of HENNING and RUBENSON[10,11] that a peripheral inhibitor of dopa-decarboxylase, DL-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)-propionic acid[12,13] (DL-HMD) reverses the hypertensive effect of L-dopa and causes accumulation of dopamine in the brain of rats. It is assumed that dopamine or norepinephrine produces a centrally mediated hypotensive action which is usually obscured by their peripheral pressor effects. The inhibition of peripheral decarboxylation of L-dopa unmasks the central hypotensive effect of its metabolites. Our recent findings in dogs support this hypothesis.

Mongrel dogs of either sex and 7–11 kg body weight were anesthetized with sodium vinbarbital, 50 mg/kg i.v. Femoral arterial pressure and heart rate were recorded continuously through a catheter and Statham model P23Db pressure transducer on Sanborn 150 polygraph. Drugs were first dissolved in 1 *N* HCl and further diluted 1:10 with physiological saline. The total volume of final drug solution was kept at 10 ml. All drugs were infused into femoral vein over a 2-min period. Control animals received 10 ml of acidified saline. Arterial pressure and heart rate were recorded at 1, 5, 15, 30, 60 and 120 min after administration of L-dopa.

[1] G. C. COTZIAS, P. S. PAPAVASILIOU and R. GELLENE, New Engl. J. Med. *280*, 337 (1969).
[2] M. D. YAHR, R. C. DUVOISIN, M. J. SCHEAR, R. E. BARRETT and M. M. HOEHN, Arch. Neurol. *21*, 343 (1969).
[3] D. B. CALNE, J. BRENNAN, A. S. D. SPIERS and G. M. STERN, Br. med. J. *1*, 474 (1970).
[4] R. DEGKWITZ, R. FROWEIN, C. KULENKAMPFF and U. MOHS, Klin. Wschr. *38*, 120 (1960).
[5] P. HOLTZ and D. PALM, Ergebn. Physiol. *58*, 1 (1966).
[6] J. M. GAILLARD, P. SCHAEPPI and R. TISSOT, Archs int. Pharmacodyn. Thér. *180*, 423 (1969).
[7] J. CONSTANTINIDIS, J. C. DE LA TORRE, R. TISSOT and F. GEISSBÜHLER, Psychopharmacologia *15*, 75 (1969).
[8] A. BERTLER, B. FALCK, C. H. OWMAN and E. ROSENGREN, Pharmac. Rev. *18*, 369 (1966).
[9] G. G. S. COLLINS and G. B. WEST, Br. J. Pharmac. *34*, 514 (1968).
[10] M. HENNING and A. RUBENSON, J. Pharm. Pharmac. *22*, 241 (1970).
[11] M. HENNING and A. RUBENSON, J. Pharm. Pharmac. *22*, 553 (1970).
[12] C. C. PORTER, L. S. WATSON, D. C. TITUS, J. A. TOTARO and S. S. BYER, Biochem. Pharmac. *11*, 1067 (1962).
[13] G. BARTHOLINI and A. PLETSCHER, J. Pharm. Pharmac. *21*, 323 (1969).

In trying to inhibit peripheral dopa decarboxylase we used L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)-propionic acid (L-HMD). The L-form was recently shown to be the active component of the racemic mixture[14]. Central inhibition of decarboxylation of aromatic amino acids was attempted with N^1-(DL-seryl)-N^2-(2,3,4-trihydroxybenzyl)hydrazine (Ro 4-4602). At 100 mg/kg and higher doses, Ro 4-4602 was reported to inhibit dopa decarboxylase in the brain of rats[15]. Both inhibitors of dopa decarboxylase were administered i.v. 5 min prior to L-dopa. The statistical significance of the changes in arterial pressure and heart rate was determined with the Student's *t*-test.

The results of our experiments are summarized in Tables I and II. In control animals saline produced no significant change in mean arterial pressure (MAP) or heart rate during the 2-h period. L-dopa produced a dose-dependent increase in MAP. L-HMD, 15 mg/kg i.v. or Ro 4-4602, 100 mg/kg i.v. alone had no significant effect on MAP. The pressor effect of L-dopa was reversed by the decarboxylase inhibitors. Pronounced hypotensive response was observed in animals treated with L-HMD + L-dopa, while only slight hypotensive effect was produced by Ro 4-4602 and L-dopa. The difference in the hypotensive response in both groups of animals (groups 6 and 9) was significant statistically ($p < 0.05$).

In animals receiving L-dopa alone at either 25 or 50 mg/kg i.v., heart rate was slowed during the maximal hypertensive response. This can be attributed to reflex bradycardia. In animals receiving L-HMD and L-dopa, in spite of lowered arterial pressure, heart rate was consistently decreased to a greater extent than in control animals in spite of lowered arterial pressure. This may indicate a centrally-induced decrease in sympathetic tone.

Our results suggest that peripheral inhibition of dopa decarboxylase with L-HMD reverses the effects of L-dopa on the arterial pressure of the anesthetized dog. By diminishing dopamine formation in the peripheral organs, cerebral blood concentration of L-dopa was probably increased. We suggest that L-HMD also effectively removed the dopa-decarboxylase blood-brain barrier enabling L-dopa to enter the brain without loss where it was metabolized since L-HMD itself does not enter the brain. Ro 4-4602 probably also removed the enzymatic blood-brain barrier to L-dopa, but Ro 4-4602 may have entered the brain along with L-dopa, inhibiting its metabolism. After pretreatment of our dogs with Ro 4-4602, L-dopa had only slight hypotensive action. It is, therefore, reasonable to assume that a central action of a decarboxylation product of L-dopa is responsible for the observed hypotensive effect. In rats, HENNING and RUBENSON[10,11] found that FLA-63, a disulfiram derivative and an inhibitor of dopamine-β-hydroxylase[16] antagonized the hypotensive effect of DL-HMD and L-dopa combination, while spiroperidol, a dopamine receptor blocking agent, failed to block the hypotensive effect. According to recent findings of BUTUZOV[17], norepinephrine administered into lateral or fourth ventricle of cat brain activates reticulospinal inhibition involved in the control of sympathetic tone. These findings suggest that L-HMD + L-dopa-induced hypotension may be mediated by norepinephrine, which reduces sympathetic tone centrally.

Zusammenfassung. Nach Vorbehandlung mit L-HMD (peripherer Hemmer der Dopa-Dekarboxylase) wird mit L-Dopa (25 und 50 mg/kg i.v.) Blutdruck und Herzfrequenz herabgesetzt.

D. H. MINSKER, A. SCRIABINE, A. L. STOKES, C. A. STONE and M. L. TORCHIANA

Merck Institute for Therapeutic Research, West Point (Pennsylvania 19486, USA), 14 December 1970.

[14] V. J. LOTTI and C. C. PORTER, J. Pharmac. exp. Ther. *172*, 406 (1970).
[15] G. BARTHOLINI, W. P. BURKARD and A. PLETSCHER, Nature, Lond. *215*, 852 (1967).
[16] T. SVENSSON and B. WALDECK, Eur. J. Pharmac. *7*, 278 (1969).
[17] V. G. BUTUZOV, Byull. exp. Biol. Med., USSR *35*, 65 (1970).

A Hypothesized Unifying Mechanism in Neural Function[1]

Considering the amount of research being conducted on the nervous system of animals and man, a working hypothesis regarding a unifying mechanism in neural function is needed. If one will consider the results from experiments with various animal nervous systems and test models, there seems to be a reasonable scientific basis for such a hypothesis. I propose that, with or without associated reduction and/or oxidation respectively, ligand complexing with exposed disulfides and/or sulfhydryls in protomers of nerve membranes may be considered as one unifying mechanism in neural function.

The probable importance of complexing, oxidation-reduction and/or one-electron-transfer mechanisms in energy transformation in living systems has been emphasized by SZENT-GYÖRGYI[2], PULLMAN and PULLMAN[3], EDGAR[4] and GREEN and BAUM[5] among others. Complex formation and electron transfer were shown in one type of energy transduction in chemoreception by certain insects[6]. In this research[6], messenger quinones (ligands) complexed with and oxidized sulfhydryls at the receptor sites associated with the dendritic branches of the sensory neurons. Experimental results from other[7] studies of receptor chemical aspects of chemoreception by animals and man appear compatible with such sulfhydryl and disulfide involvement. The importance[8] of the –SH group and –S–S– bond in the basic function of the acetylcholine receptor lends essential support to the hypothesis. The widespread occurrence[2] of such groups and bonds in macromolecules which apparently influence conformational states of protomers in various other biological membranes also suggests a basic role for them.

A normal basic function in a nervous system involves the highly ordered transmission of energy through and between nerve cells; this being especially regulated by membranes and associated intra- and extra-cellular molecules and ions. This rigorously channeled energy must be rapidly and repeatedly converted from molecular to ionic form, and vice versa, such that a) energy transductions in receptor macromolecules occur; b) action potentials are generated in and conducted through neurons; c) synaptic transmissions result; and d) learning may occur and learned information is stored and can be retrieved. Experimental evidence that each of the above