sented here and previously (*2*) have led to the concept that variations in contact between the elements of the JG apparatus may be responsible for the control of renin secretion and that supporting evidence for both theories may be unified by this model.

With regard to the macula densa theory, many physiologists interpret their data as indicating that lowered sodium transport through the distal tubule increases renin secretion (*5*). A smaller sodium load in the distal tubule would probably be accompanied by a decrease in its volume and therefore decreased contact with granular cells (Fig. 2A). Consistent with this line of reasoning we can propose that less contact leads to an increase while more contact would decrease renin secretion. This mechanism also fits the stretch receptor theory which is based on the fact that lowering the blood volume passing through the arterioles increases renin secretion and vice versa. The same mechanism involving reversible contact as a key factor could be involved; a larger arteriolar volume would increase the contact and decrease the renin secretion, whereas a smaller volume would decrease the contact and increase renin secretion (Fig. 2B).

Although the basic mechanisms are still unknown, it is probable that whatever chemical influence the distal tubule exerts on the granular cells will be altered by changes in contact. We can further speculate that sodium itself might be the critical link in controlling renin secretion. Teleologically this makes good sense since the renin-angiotensin-aldosterone system acts to conserve sodium. Larger areas of contact would increase the sodium delivered by the distal tubule to the granular cells, and the greater sodium transport or concentration would then act to decrease renin secretion. Conversely, decreased contact would produce the opposite effects.

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Dopamine: Stimulation-Induced Release from Central Neurons

Abstract. *Dopamine, synthesized in rat brain slices from labeled* L-*tyrosine or* L-*dopa, can be released by electrical stimulation of a type known to induce neuronal depolarization. Pretreatment of the animals with 6-hydroxydopamine, which destroys central catecholamine-containing nerve terminals, substantially reduced the release of dopamine synthesized from [^{14}C]tyrosine or from a low concentration of [^{3}H]dopa, whereas the release of dopamine formed from a high concentration of [^{3}H]dopa remained essentially unchanged. The observations that at high concentrations* L-*dopa may enter noncatecholaminergic cells, undergo decarboxylation to dopamine, and subsequently be liberated in response to depolarization suggest that dopamine may act as a substitute central transmitter, possibly in serotonergic neurons. This mechanism may contribute to* L-*dopa's clinical effects in parkinsonian patients.*

Considerable evidence suggests that dopamine may serve as a neurotransmitter in certain neural pathways within the mammalian central nervous system (*1*). Dopamine occurs in high concentrations within the terminals of some neurons together with enzymes for its synthesis and degradation (*2*), and its microiontophoretic application influences the firing patterns of specific neurons (*3*). Furthermore, indirect evidence of cerebral dopamine release following stimulation has been obtained from various in vivo experiments (*4*). We now report that dopamine formed in cerebral tissues in vitro from labeled tyrosine or L-dopa can be released by procedures which induce nerve cell depolarization. At relatively high L-dopa concentrations, dopamine release appears to derive from noncatecholaminergic as well as catecholamine-containing neurons.

Observations both in vitro and in vivo indicate that exogenous catecholamines may be actively taken up by cerebral tissues, where they mix with endogenous amine stores (*5*). It has previously been observed that labeled dopamine accumulated by brain slices may be liberated by electrical field stimulation (*6*). Although most exogenous catecholamines are taken up specifically, it appears that some uptake may also occur in noncatecholaminergic cells, especially at high amine concentrations (*7*). In an attempt to examine this possibility further, as well as to approximate the situation in patients treated with high doses of L-dopa, we have studied the stimulation-induced release of dopamine formed from labeled precursors in brain slices obtained from normal rats and from rats in which most catecholaminergic neurons had been destroyed by pretreatment with 6-hydroxydopamine.

Striatal slices weighing approximately 10 mg prepared from the brains of adult, male Sprague-Dawley rats were used in all experiments. After incubation for 30 minutes at 37°C in a supplemented Krebs-Ringer medium saturated with 5 percent CO_2 in O_2 and containing [^{14}C]tyrosine (0.4 curie/mmole; $2 \times 10^{-6} M$) or L-[^{3}H]-dopa (23.5 curie/mmole; $1 \times 10^{-7} M$ or $1 \times 10^{-4} M$), slices were placed between platinum coil electrodes in individual superfusion chambers (*8*). After 40 minutes of superfusion with fresh, oxygenated medium (150 μl/min), when the spontaneous efflux of radioactivity had fallen to a nearly steady level, rectangular, d-c, pulsatile stimulation (10 ma, 100 hertz, 4.0 msec) was applied for 1 minute, with a Grass S-4 stimulator and CCU-IA constant current control unit. Serial fractions of effluent medium were collected immediately before and during electrical stimulation in chilled vials containing 0.001 percent tyrosine, dopa, and dopamine in 2*N* HCl. Assays for labeled dopamine and its deaminated, *O*-methylated metabolites in the effluent superfusate or in tissue homogenates were carried out by adsorption chromatography through alumina (*9*) and Dowex-50 (Na^+ form) (*10*).

Table 1. Effect of 6-hydroxydopamine pretreatment on stimulation-induced release of dopamine synthesized from labeled precursors. Rats received three doses of 200 μg of 6-hydroxydopamine hydrobromide intracisternally at 48-hour intervals 4 to 6 weeks prior to use.

Precursor*	Release†		
	Untreated	6-Hydroxydopamine	Percent of control
[^{14}C]Tyrosine ($2 \times 10^{-6}M$)	351 ± 14	95 ± 21	27.0 ± 6
[^{3}H]Dopa ($10^{-7}M$)	526 ± 95	242 ± 62	51.7 ± 6
[^{3}H]Dopa ($10^{-4}M$)	831 ± 85	720 ± 80	86.6 ± 10

* Slices of striatum were incubated for 30 minutes in a physiologic medium containing a labeled precursor in the given concentration. † Each result is the mean (± S.E.M.) for six or more slices reported in counts per minute per milliliter of effluent.

Electrical stimulation resulted in a fivefold or greater rise in the efflux of labeled dopamine from slices previously incubated with [^{14}C]tyrosine or [^{3}H]-dopa (Fig. 1). The concomitant efflux of metabolites, which increased between two- and fourfold, consisted principally of noncatechol and deaminated noncatechol products (presumably methoxydopamine and homovanillic acid). Under the condition of these experiments, no significant release of radioactivity attended electrical stimulation of slices previously incubated with [^{14}C]urea. The results are similar to those found in slices incubated with [^{3}H]norepinephrine (*11*) or [^{3}H]serotonin (*8*) and support the contention that the monoamines are discharged from central neurons during nerve terminal depolarization.

Since tyrosine hydroxylase, the enzyme mediating the conversion of tyrosine to dopa, is confined exclusively to catecholamine-containing cells, the release of labeled dopamine from slices incubated with [^{14}C]tyrosine presumably occurs from neurons which naturally contain dopamine (*12*). This may not be true in the case of dopamine formed from exogenous L-dopa. Aromatic amino acid decarboxylase, which mediates the conversion of dopa to dopamine, occurs in serotonergic as well as catecholamine-containing neurons. Furthermore, previous observations suggest that exogenous L-dopa may be taken up and decarboxylated to dopamine in serotonergic neurons (*13*). In order to estimate the amount of dopamine released from cells not containing catecholamine, some rats were pretreated with 6-hydroxydopamine, which selectively destroys catecholaminergic neurons (*14*). These animals received three intracisternal injections of 200 μg of 6-hydroxydopamine hydrobromide (164 μg free base) at 48-hour intervals, 4 to 6 weeks prior to use. Control rats received an equal volume (20 μl) of the vehicle solution (0.01 percent ascorbic acid in normal saline, adjusted to *p*H 4.3). 6-Hydroxydopamine pretreatment led to a marked diminution in the formation of dopamine in striatal slices incubated with [^{14}C]tyrosine (35 ± 6 percent of control) but did not significantly alter synthesis in slices incubated with high ($10^{-4}M$) or low ($10^{-7}M$) concentrations of [^{3}H]dopa.

The electrically induced release of [^{14}C]dopamine formed from [^{14}C]-tyrosine or of [^{3}H]dopamine synthesized from low concentrations of [^{3}H]dopa was markedly diminished by 6-hydroxydopamine pretreatment (Table 1). The decreased release (by 73 percent) of dopamine formed from tyrosine in slices from animals pretreated with 6-hydroxydopamine appears to be a consequence of destruction of catecholaminergic terminals, since the formation of dopamine from tyrosine was similarly reduced. At low concentrations of [^{3}H]dopa, dopamine synthesis did not appear to be inhibited by pretreatment with 6-hydroxydopamine (97 ± 5 percent of control), but there was decreased release by electrical stimulation (Table 1). These observations suggest that at this concentration of dopa ($10^{-7}M$) considerable dopamine formation occurs in cellular elements (possibly glia, pericytes, or dopaminergic terminals whose release mechanisms are impaired by 6-hydroxydopamine) which do not respond to electrical stimulation with release of their dopamine. On the other hand, the stimulation-induced release of [^{3}H]dopamine formed from a high concentration of L-[^{3}H]dopa ($10^{-4}M$) was not appreciably reduced by 6-hydroxydopamine (Table 1). This finding would suggest that high concentrations of L-dopa may be required for significant uptake into nondopaminergic neurons. Recent histochemical observations are consistent with this interpretation (*15*). Since serotonergic neurons do not appear to be significantly affected by 6-hydroxydopamine in the doses used (*13*), our results further support the hypothesis that at high levels of exogenous L-dopa, decarboxylation may occur in serotonergic or perhaps other aromatic amino acid decarboxylase–containing cells and that the dopamine thus formed can be released by procedures which induce nerve terminal depolarization.

The mechanisms by which L-dopa produces therapeutic as well as deleterious effects in parkinsonian patients are of theoretical interest and practical concern. Beneficial clinical response deriving from the use of large doses of L-dopa have been presumed to reflect the replenishment of dopamine stores in striatal dopaminergic neurons. Ad-

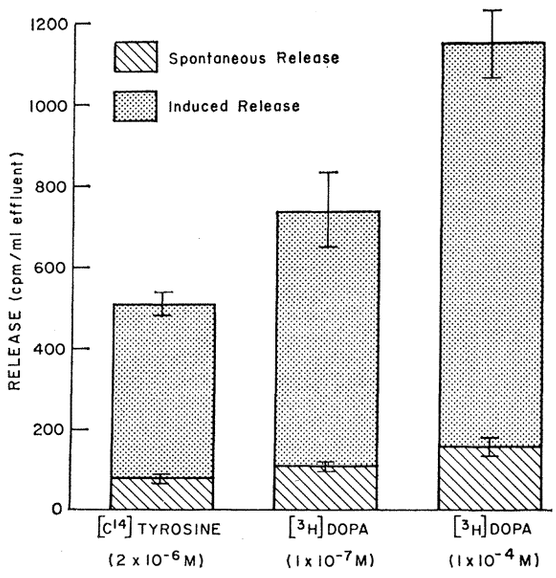

Fig. 1. Release of radioactive dopamine from rat striatal slices. Tissues were incubated with labeled precursors for 30 minutes, superfused, and stimulated. Lined areas of the bars indicate spontaneous dopamine efflux in 1 ml of effluent collected during the 6-minute interval just before stimulation, and the total height of each bar depicts dopamine efflux in 1 ml of effluent collected during the succeeding 6-minute interval which included stimulation. The dotted areas thus represent stimulation-induced release. Each result is the mean (± S.E.M.) expressed as counts per minute per milliliter of effluent for six or more slices.

vanced disease, however, which is attended by a degeneration of most nigro-striatal dopaminergic neurons, does not appear to diminish L-dopa's therapeutic efficacy. Lloyd and Hornykiewicz (*16*) have found that dopa decarboxylase levels in the striatum of parkinsonian patients is low, but enzyme activity is still present (5 to 10 percent of normal). The site of this enzyme activity was not determined and could represent aromatic amino acid decarboxylase in serotonergic neurons. Uptake of dopa into serotonergic or other central neurons containing aromatic amino acid decarboxylase with subsequent conversion to dopamine and release as a "false" transmitter might contribute to clinical changes occurring in patients receiving high doses of this amino acid.

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A Male-Producing Strain of the House Fly

Abstract. *An autosome inherited by male offspring only and a temperature-sensitive lethal factor have been combined in a house fly strain which produces both male and female progeny when reared at 25.6°C but only male progeny when reared at 33.3°C.*

The sterility principle of insect control has received much attention since sterile males were used successfully in screwworm eradication programs in the United States (*1*). Theoretical models (*2*) and preliminary tests (*3*) have indicated the feasibility of using this same principle in control programs against the house fly, *Musca domestica* L. It would be valuable to eliminate the need for sexing adult house flies in any program that involves the field release of sterile males. House flies are currently sexed by hand or through the use of mechanical devices (*4*) which are not 100 percent efficient. This report discusses the development of a genetic technique for obtaining only male progeny from a house fly strain that can be maintained routinely in the laboratory.

The male-producing strain (*MP*) was constructed by means of matings between wild-type house flies from Gainesville, Fla., and house flies that carry a recessive temperature-sensitive lethal factor (*tsl*) on autosome III. The *tsl* factor was recovered in tests at this laboratory by rearing particular autosome III homozygotes at "cold" or "hot" temperatures. House flies homozygous for *tsl* can be reared successfully at 25.6°C but die in the late larval or pupal stage when reared at 33.3°C. The Gainesville strain is unusual because both male and females possess an XX sex chromosome complement and no apparent Y chromosome can be observed in cytological preparations (*5*). More commonly, female house flies are XX whereas males are XY with the Y chromosome determining maleness. However, the important feature of the Gainesville strain in regard to producing *MP* house flies is that Gainesville males generally show holandric inheritance for one member of the third pair of autosomes; that is, one member is transferred exclusively from a male parent to its male progeny as though it were linked to a male determiner or a Y chromosome. Thus, all *MP* females are homozygous for the *tsl* factor on autosome III whereas all males are heterozygous for *tsl* against its holandrically inherited *tsl* + (wild-type) allele. Heterozygosity for the *tsl* factor is made permanent in males because crossing over does not occur in the male. When progeny from the *MP* strain are reared at 25.6°C, both males and females are produced. However, when they are reared at 33.3°C, only males emerge (Table 1).

Table 1. Results of rearing house flies of the *MP* strain at 25.6° and 33.3°C.

Temperature (°C)	Males (No.)	Females (No.)
33.3	1022	0
25.6	512*	472

* The *MP* males generally produced in slight excess of females.

An additional advantage of the *MP* strain is that the holandrically inherited third autosome can be extracted from appropriate field populations and combined with the *tsl* factor in two generations. Thus, the debilitating effects of laboratory rearing and inbreeding can be minimized in obtaining *MP* males for field release. Moreover, increased temperatures tend to decrease house fly rearing time within certain limits (*6*).

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