PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **155**, 305-307 (1977)

The Effect of Prostaglandins on the Release of [^{3}H]Dopamine from Superfused Slices of Rat Striatum following Electrical Stimulation[1] (39795)

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It is now well established that several neurohumoral and humoral substances can influence the release of norepinephrine from peripheral adrenergic neurons following nerve stimulation (1-6). These substances appear to act on receptors located on the terminal varicosities of adrenergic neurons (7). Although the pharmacological significance of these presynaptic receptors is of great importance, the exact physiological significance of these various receptors is unclear. They appear to be very important in helping to locally regulate the release of the neurotransmitter.

Similar kinds of local regulation of neurotransmitter release have been observed for some neurons in the central nervous system. For instance, norepinephrine (NE) can cause autoinhibition of its own release from superfused slices obtained from rat occipital cortex via an action on α receptors (8, 9). A similar phenomenon has been demonstrated for dopamine in the rat neostriatum (9, 10). Similarly, there is some indication that prostaglandins may also influence the release of NE and dopamine from brain slices although very few data are available (11, 12). The purpose of this study was to investigate the action of prostaglandins on the release of dopamine following electrical stimulation of neostriatal slices. The results suggest that prostaglandins of the E series can modulate the release of dopamine following electrical stimulation but the effect is small compared to that seen in peripheral adrenergic structures.

Methods. Preparation of slices. Male Sprague-Dawley rats weighing approximately 200-250 g were killed by decapitation, their brains were immediately removed, and the striatum were rapidly dissected out with glass manipulators at 4°. The isolated striatum were then sliced to thicknesses of 0.7 mm with a McIlwain tissue chopper. The slices were placed in minivials containing 1.9 ml of Krebs-Ringer bicarbonate medium containing in millimolar concentrations: NaCl, 118.6; $NaHCO_3$, 25.0; KCl, 4.8; KH_2PO_4, 1.2; $CaCl_2$, 2.5; $MgSO_4$, 7; H_2O, 1.2; glucose, 11.1. The slices were then incubated with 10 μCi of [^{3}H]dopamine (sp act 6.1 Ci/mmole; total concentration 8×10^{-7} M) for 30 min in an atmosphere of 90% O_2-5% CO_2. Individual slices were then placed in specially prepared glass chambers jacketed with warm water at 37°. The slices were held in place between two platinum mesh grids and superfused with fresh buffer at a rate of 1.0 ml/min with Buchler peristaltic pumps. The total volume of the chambers was 2 ml.

Application of drugs and stimulation. The slices were superfused for 10 min with normal buffer and then switched to a buffer containing various concentrations of prostaglandin E_1, E_2, or $F_{2\alpha}$. Following 30 min of superfusion, the slices were stimulated for 2 min with biphasic square-wave pulses at various frequencies (10, 50, or 100 Hz) of 1.1-msec duration at an intensity of 10 V by means of two glass stimulators.

The wave forms, intensity, and duration of the electrical pulses were continuously monitored by an EV-70 Heath dual-trace oscilloscope. Superfusate effluents were collected at 10-min intervals in iced tubes containing a protective solution consisting of sodium metabisulfite, 1 mg/ml, disodium EDTA, 2 mg/ml, and 2 N hydrochloric acid, 2 ml. An aliquot was taken for determination of total ^{3}H and the remaining sample was processed for separation of [^{3}H]dopamine and ^{3}H-labeled metabolites.

Separation of labeled dopamine and metabolites. Samples were processed by alumina and column chromatography (Dowex

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[1] Supported in part by U.S. Public Health Service Grant NS 10260 and The Council for Tobacco Research, U.S.A.

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ISSN 0037-9727

50) according to the procedure described by Westfall *et al.* (13). The recovery of dopamine through both columns was routinely 70%. Samples have not been corrected for this recovery.

Calculation of data. The release of [^{3}H]-dopamine was calculated from the formula, $[(A - B)/(A + B + C)] \times 100$, and was expressed as the stimulation-induced overflow of [^{3}H]dopamine as a percentage of the total [^{3}H]dopamine in the tissue at the onset of the stimulation. A = total outflow during stimulation; B = estimated spontaneous outflow; $A - B$ = stimulation-induced overflow. C = [^{3}H]DA in the tissue at the onset of stimulation; this was calculated by adding the [^{3}H]DA outflow and the [^{3}H]DA content in the tissue at the end of superfusion. Statistical analysis of data was calculated using Student's t test on an Olivetti program calculator.

Results. The effect of various frequencies of electrical stimulation (total stimulation time 2 min) on the release of [^{3}H]dopamine is depicted in Fig. 1. A very flat frequency-response curve is is seen, with 50 Hz producing a nearly maximal increase in [^{3}H]DA release. A similar increase in ^{3}H-labeled metabolites was also seen during the following electrical stimulation, although there was a much greater percentage increase in [^{3}H]dopamine (fivefold as compared to twofold for [^{3}H]dihydroxyphenylactic acid, [^{3}H]HVA, and [^{3}H]dihydroxyphenylglycol). Both PGE$_1$ and PGE$_2$, added 20 min prior to and during electrical stimulation, produced a significant reduction in [^{3}H]DA release at all three frequencies, although the inhibition was most pronounced at a frequency of 10 Hz.

The effect of two concentrations of PGE$_1$ and PGE$_2$, as well as PGF$_{2\alpha}$, on the release of [^{3}H]dopamine induced by 50 Hz for 2 min is shown in Fig. 2. It can be seen that 10^{-7} M concentrations of both PGE$_1$ and PGE$_2$ also produced a significant inhibition, while PGF$_{2\alpha}$ (10^{-6} M) was without effect in altering the release.

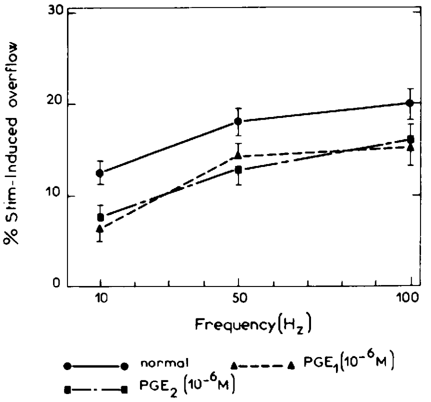

FIG. 1. The effect of various electrical frequencies (10, 50, and 100 Hz) on the percentage of stimulation-induced overflow of [^{3}H]dopamine from normal superfused rat striatal slices or slices superfused in the presence of PGE$_1$ or PGE$_2$ (10^{-6} M). All slices were stimulated for a total of 2 min. Each point is the mean ± SEM of at least five slices.

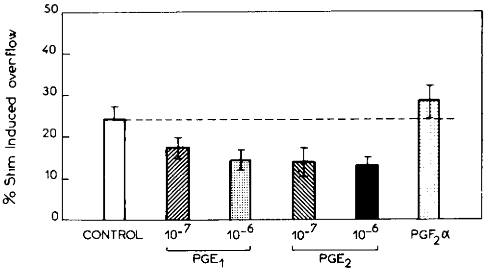

FIG. 2. Effect of PGE$_1$, PGE$_2$, and PGF$_{2\alpha}$ on the stimulation-induced release of [^{3}H]dopamine following electrical stimulation with biphasic square-wave pulses (50 Hz, 1.1-msec duration, 10-V intensity, 2-min total stimulation time). Each bar is the mean ± SEM of at least five slices.

In another series of experiments rats were pretreated for 3 days with indomethacin, 5 mg/kg/day sc, prior to electrical stimulation of the slices. There was an increase in the stimulation-induced release of [^{3}H]dopamine from 24.5 ± 2.5 in slices from untreated animals compared to 34.3 ± 3.2 in slices obtained from indomethacin-treated animals ($P < 0.05$).

Discussion. In addition to the inhibition of the electrically induced release of NE from adrenergic neurons seen with α agonists (2, 3, 14–16), acetylcholine (5, 21), and dopamine (19, 20), a similar inhibition has been observed following the administration of prostaglandin E$_1$ or E$_2$ (4, 17, 18). This has led to the hypothesis that prostaglandins of the E series are involved in the normal local regulation of NE release following sympathetic nerve stimulation.

The present results demonstrate that prostaglandins of the E series, but no F$_{2\alpha}$, can similarly depress the release of $[^3H]$dopamine induced by electrical field stimulation of striatal slices. This is consistent with the report of Bergström *et al.* (11), who showed that PGE_2 produced a slight inhibition of total ^3H from neostriatal slices. PGE_1 also appears to decrease the release of NE from cerebral occipital cortex (12). Therefore, at least two central monoaminergic structures respond to prostaglandins in a manner similar to peripheral noradrenergic synapses. It should be noted, however, that the effects of PGE_1 and PGE_2 observed in the present report are small compared to those reported from peripheral adrenergic structures.

Similar to the inhibition of the electrically induced release of dopamine by prostaglandins reported in the present study, dopaminergic as well as muscarinic agonists have been shown to decrease the electrically and drug-induced release of $[^3H]$dopamine from striatal slices (13, 22, 23). In contrast, no inhibition of dopamine release has been observed following the administration of α- or β-adrenergic agonists (24). A similar unequal number of presynaptic receptors has been reported for noradrenergic neurons in the cortex (12). Noradrenergic neurons in this tissue appear to have both presynaptic α and prostaglandin receptors but lack muscarinic, dopaminergic, and α-adrenergic receptors (12). These results suggest that selective mechanisms for the local control of dopamine and norepinephrine release may be present in the central nervous system.

Summary. It is concluded that prostaglandins of the E series, but not $F_{2\alpha}$, can decrease the electrically induced release of $[^3H]$dopamine from rat striatal slices. The effect is much less dramatic than that seen on peripheral adrenergic neurons. Prostaglandins may play a role in helping to modulate the release of dopamine following nerve stimulation.

The authors wish to thank Ms. Georgia Wahl and Joann Sanders for excellent technical assistance. Thanks are also extended to Dr. John Pike, Upjohn Company, for generous supplies of PGE_1 PGE_2, and $PGF_{2\alpha}$.

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Received September 1, 1976. P.S.E.B.M. 1977, Vol. 155.