From: Tepper, J.M., Sawyer, S.F., Nakamura, S., & Groves, P.M. (1991) Dopaminergic and serotonergic terminal excitability: Effects of autoreceptor stimulation and blockade. In: J.J. Feigenbaum and M. Hanani (Eds.) The Presynaptic Regulation of Neurotransmitter Release: A Handbook, Tel Aviv, Freund Publishing Co., pp. 523-550.

CENTRAL DOPAMINERGIC AND SEROTONERGIC TERMINAL EXCITABILITY: EFFECTS OF AUTORECEPTOR STIMULATION AND BLOCKADE

J.M. Tepper[1], S.F. Sawyer[2,4], S. Nakamura[3] and P.M. Groves[2]

[1] *Center for Molecular and Behavioral Neuroscience*
Rutgers, The State University of New Jersey
Newark, NJ 07102

[2] *Departments of Psychiatry and Neuroscience*
University of California, San Diego
La Jolla, CA 92083

[3] *Department of Physiology*
Faculty of Medicine
Kanazawa University
Kanazawa 920, Japan

[4] *Present Address:*
Department of Cell Biology and Anatomy
University of Texas
Southwestern Medical Center at Dallas
Dallas, TX 75235

1. INTRODUCTION

Many biochemical studies, mostly carried out *in vitro*, have provided evidence suggesting the presence of inhibitory autoreceptors located at the terminals of central dopaminergic and serotonergic neurons that modulate transmitter release from presynaptic nerve endings. As described more fully elsewhere in this volume, the stimulation of these autoreceptors by the appropriate agonists, e.g., apomorphine or dopamine (DA) itself for DA neurons, or 5-methyoxy-N-N-dimethyltryptamine (5-MeODMT) or lysergic acid diethylamide (LSD) for serotonergic (5-HT) neurons, leads to an inhibition of electrically or potassium-evoked transmitter release from brain slices or synaptosomes. Conversely, autoreceptor blockade by appropriate antagonists results in increases in evoked release (Farnebo and Hamberger, 1971; Langer, 1977; Starke et al., 1978; Gothert and Wenheimer, 1979; Baumann and Waldmeier, 1981; see Chesselet, 1984, and Moret, 1982, for recent reviews). Although it has been demonstrated in these studies that only the calcium-dependent, stimulus-evoked release of monoamines is subject to modulation by presynaptic receptors (Kamal et al., 1981; Gothert, 1980; Langer and Moret, 1982), the physiological mechanisms linking autoreceptor activation to inhibition of release are difficult to infer from studies of this kind. Furthermore, since most of the information we have concerning autoinhibition of transmitter release is derived from *in vitro* preparations, it has been difficult to demonstrate a physiologically relevant role for these receptors in the living brain.

In the preceding chapter (Nakamura et al., this volume) an *in vivo* electrophysiological method was described for investigating changes in the excitability of the cortical terminals of central noradrenergic locus coeruleus neurons as a result of the stimulation or blockade of presynaptic opiate receptors and autoreceptors (Nakamura et al., 1981; Nakamura et al., 1982a; Nakamura et al., 1982b). This method has provided direct evidence for the role of autoreceptors and presynaptic receptors in modulating monoamine release *in vivo* (Tepper et al., 1985), as well as new insights into the mechanisms whereby presynaptic receptor activation produces inhibition of transmitter release (Ryan et al., 1985b; Tepper, et al., 1987). We have applied the same techniques to a comprehensive study of autoreceptor-mediated effects at the neostriatal terminals of substantia nigra dopamine neurons (Groves et al., 1981; Tepper et al., 1984a; Tepper et al., 1984b; Tepper et al., 1986). Preliminary results have also been obtained from striatally projecting dorsal raphé serotonergic neurons (Sawyer et al., 1985) and from cortically projecting ventral tegmental area dopaminergic neurons as well (Gariano et al., 1989).

In this chapter we will review the electrophysiological pharmacology of autoreceptor-mediated effects at the terminals of central dopaminergic and

serotonergic neurons, and provide evidence that these autoreceptors modulate transmitter release *in vivo* through actions on the electrical properties of the presynaptic terminal membranes. The *in vivo* conditions under which terminal autoreceptors function will be addressed. We will conclude with a discussion of the interpretation of changes in terminal excitability, and suggest mechanisms whereby autoreceptor and other presynaptic receptor stimulation leads to changes in evoked transmitter release in central noradrenergic, dopaminergic and serotonergic neurons.

2. DOPAMINERGIC AND SEROTONERGIC TERMINAL EXCITABILITY

2.1 Effects of Autoreceptor Agonists

A detailed description of the experimental methods for measuring autoreceptor-mediated changes in terminal excitability may be found in the previous chapter and elsewhere (Groves et al., 1981; Nakamura et al., 1981; Tepper et al., 1984a,b). Briefly, terminal excitability is quantified by measuring the frequency of antidromic responses elicited from a neuron's terminal region as a function of the stimulus current. These results can be expressed by plotting stimulus current against the proportion of trials on which an antidromic response occurred. These plots are analogous to dose-response curves, in which shifts to the right in the curves following some treatment indicate decreased excitability, while shifts to the left signify increases in terminal excitability. Much of the data in this chapter will be presented in this form.

Local infusions of the DA autoreceptor agonist, apomorphine (1-10 μM, 300 nl), into dopaminergic terminal fields in the neostriatum produce a marked, dose-dependent decrease in the terminal excitability of nigrostriatal DA neurons (Tepper et al., 1984a), as shown in Figure 1A. Similarly, neostrial infusion of the 5-HT autoreceptor agonist, 5-MeODMT (10-50 μM), produces a decrease in the terminal excitability of dorsal raphe-neostriatal serotonergic neurons (Sawyer et al., 1985), as shown in Figure 2A. In central monoamine neurons, agonist-induced decreases in excitability obtain only at the nerve terminal. If excitability is tested from more proximal, pre-terminal regions of dopaminergic or serotonergic axons in the medial forebrain bundle (MFB), neither systemic nor local administration of appropriate autoreceptor agonists affects excitability at these sites, as illustrated in Figures 1B and 2B (Groves et al., 1981; Takeuchi et al., 1982; Tepper et al., 1984a; Sawyer et al., 1985).

Local infusion of amphetamine (1-10 μM: 300 nl) into DA terminal fields in the neostriatum (which acts to increase the extracellular concentration of endogenous catecholamines by increasing release and blocking reuptake),

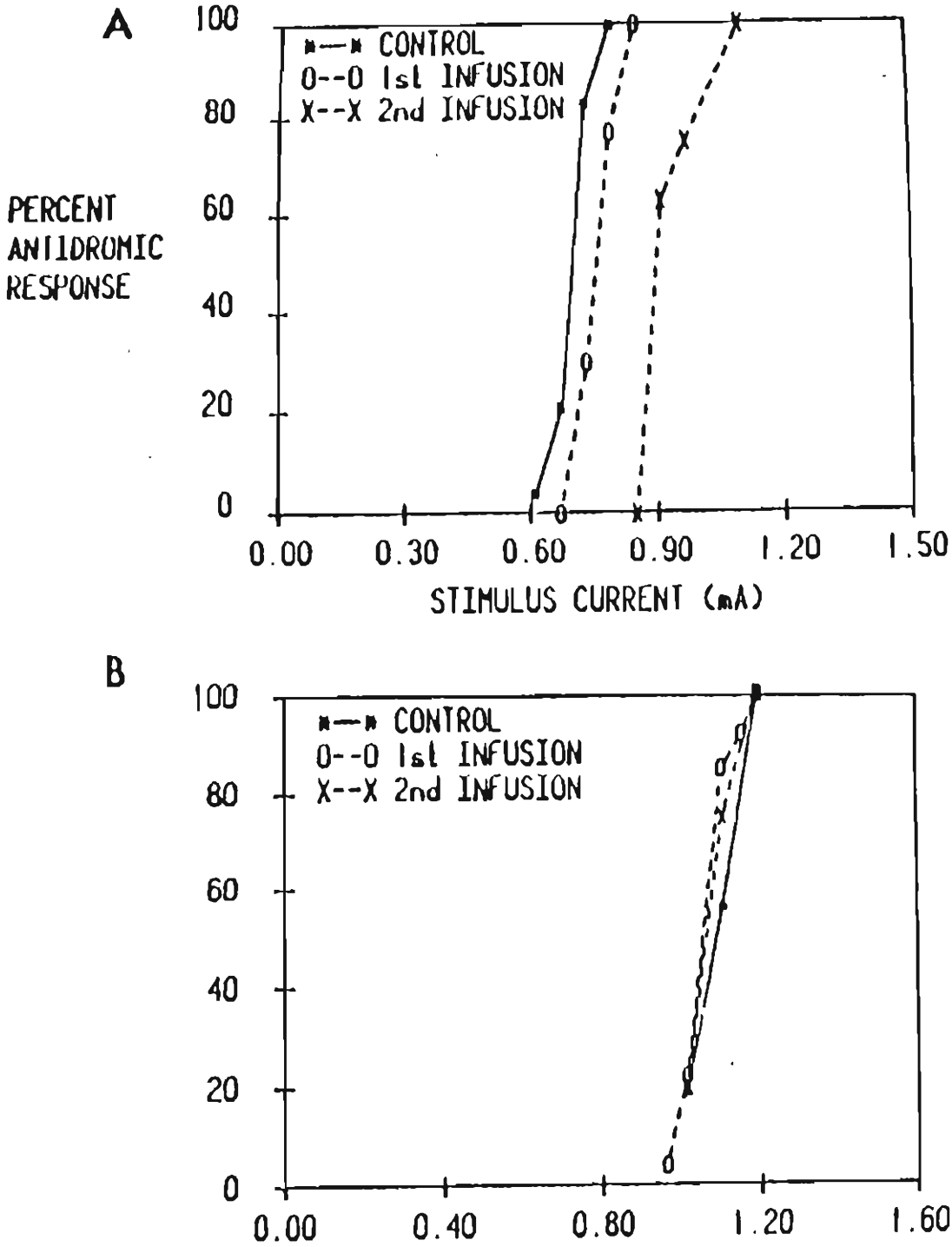


Fig. 1: A. Local infusion of the dopamine autoreceptor agonist, apomorphine (10 μM, 300 nl), into dopaminergic terminal fields in neostriatum causes a marked, dose-dependent decrease in terminal excitability of a nigral neuron, as indicated by the successive shifts to the right in the current-response curve. B. Identifical infusions into pre-terminal regions of a dopamine axon in the medial forebrain bundle (MFB) fail to alter excitability from this more proximal site. (Data in A redrawn from Tepper et al., 1984, with permission.)

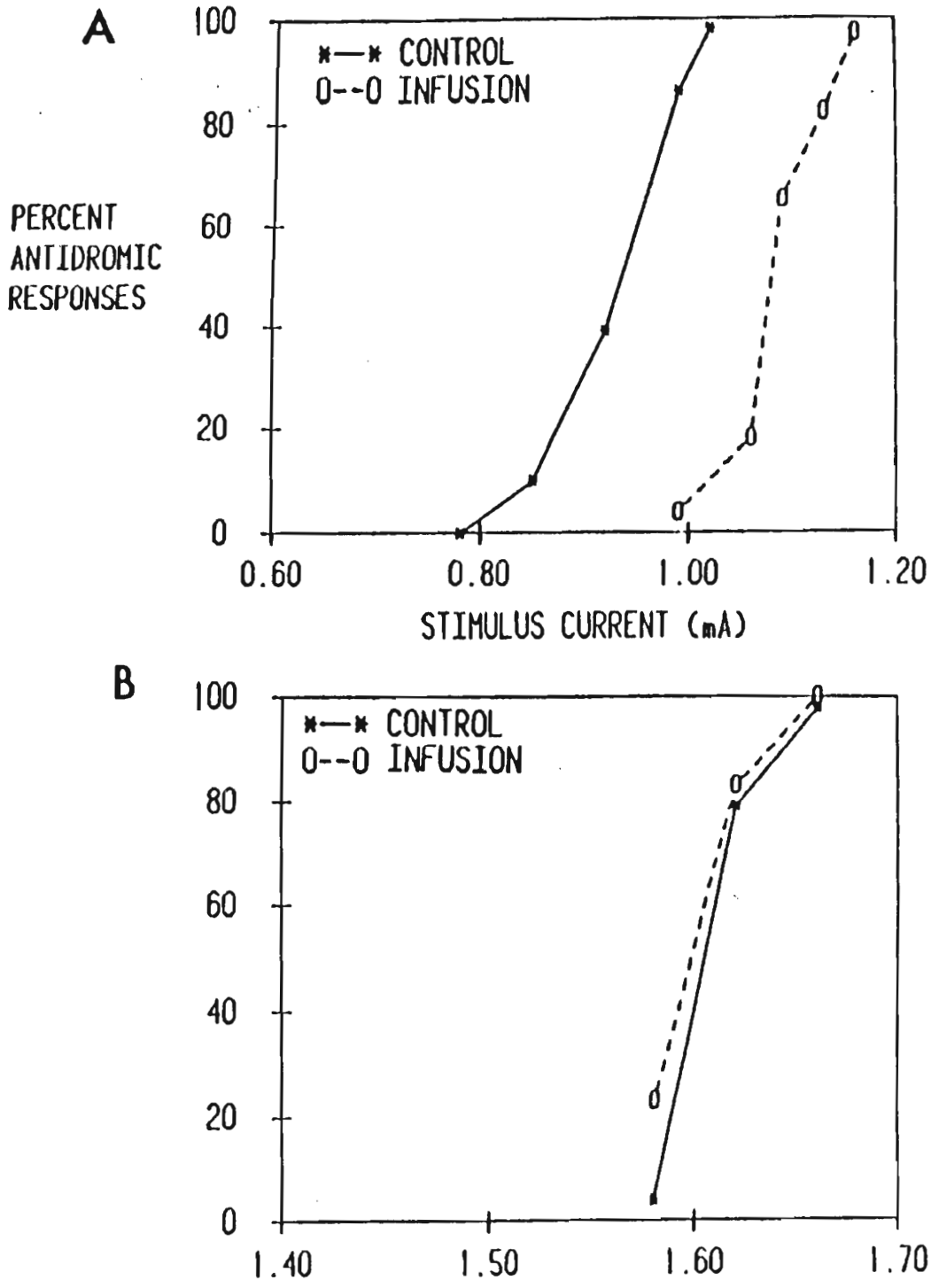


Fig. 2: A. Local infusion of the serotonin autoreceptor agonist, 5-MeODMT (10 μM, 300 nl), into serotonergic terminal fields in neostriatum causes a marked decrease in terminal excitability of a dorsal raphe neuron, as indicated by the shifts to the right in the current-response curve. B. Identical infusion into pre-terminal regions of a serotonergic axon in the MFB fails to alter excitability from this more proximal site.

leads to marked decreased in dopaminergic terminal excitability, as shown in Figure 3A (Tepper et al., 1984a). This is analogous to its effects on noradrenergic terminal excitability as described in the preceding chapter (Nakamura et al., 1982a). Similar effects are obtained following the local application of amphetamine to the terminal fields of other DA pathways including the meso-accumbens (Mereu et al., 1985) and meso-prefrontal cortical systems (Gariano et al., 1989; Tepper et al., 1987). These effects of amphetamine can be prevented by depletion of endogenous DA by pretreatment with alpha-methyl-p-tyrosine, as illustrated in Figure 3B (Tepper et al., 1984a). Thus, under appropriate conditions, e.g., increased extracellular levels of DA induced by amphetamine, endogenous as well as exogenous autoreceptor agonists produce decreased terminal excitability.

Although they act similarly, the autoreceptors on monoamine neurons are pharmacologically distinct. For example, despite its efficacy at inhibiting the release of norepinephrine and decreasing noradrenergic terminal excitability and firing rate as shown in the preceding chapter, the alpha-$_2$ adrenoceptor agonist, clonidine, does not affect the evoked release of DA, or dopaminergic terminal excitability, as shown in Figure 4.

Both amphetamine- and apomorphine-induced decreases in dopaminergic terminal excitability can be reversed or prevented by local or intravenous administration of one of a number of DA receptor agonists including haloperidol, fluphenazine and the DA D-$_2$ receptor-specific antagonist, sulpiride (Takeuchi et al., 1982; Tepper et al., 1984a; Mereu et al., 1985; Gariano et al., 1989).

These data indicate that the decreased terminal excitability in dopaminergic neurons resulting from administration of amphetamine or apomorphine reflects a specific receptor-mediated event. The blockade of the amphetamine effect by depletion of endogenous DA, the lack of effect of clonidine, and the specific antagonism of amphetamine- and apomorphine-induced decreases in terminal excitability by DA antagonists, including sulpiride, indicate that the receptor mediating these effects at the nerve terminal is pharmacologically equivalent to the D-$_2$ DA autoreceptor that controls the autoinhibition of DA release *in vitro* and *in vivo* (Kamal et al., 1981; Helmreich et al., 1982; Boyar and Altar, 1987), and the release of DA and firing rate of DA neurons *in vivo* (Pickler et al., 1987; Aghajanian and Bunney, 1977).

Similarly, 5-MeODMT-induced decreases in serotonergic terminal excitability are blocked or attenuated by the co-administration of the serotonin receptor antagonist, methiothepin, as shown in Figure 5. In serotonergic neurons, the antagonism of the effects of 5-MeODMT by methiothepin is consistent with previous observations that this drug is a potent antagonist of terminal autoreceptor-mediated inhibition of 5-HT release (Moret, 1985). Biochemical release studies indicate that the pharmacological profile of the terminal autoreceptor of serotonergic neurons closely resembles that of the

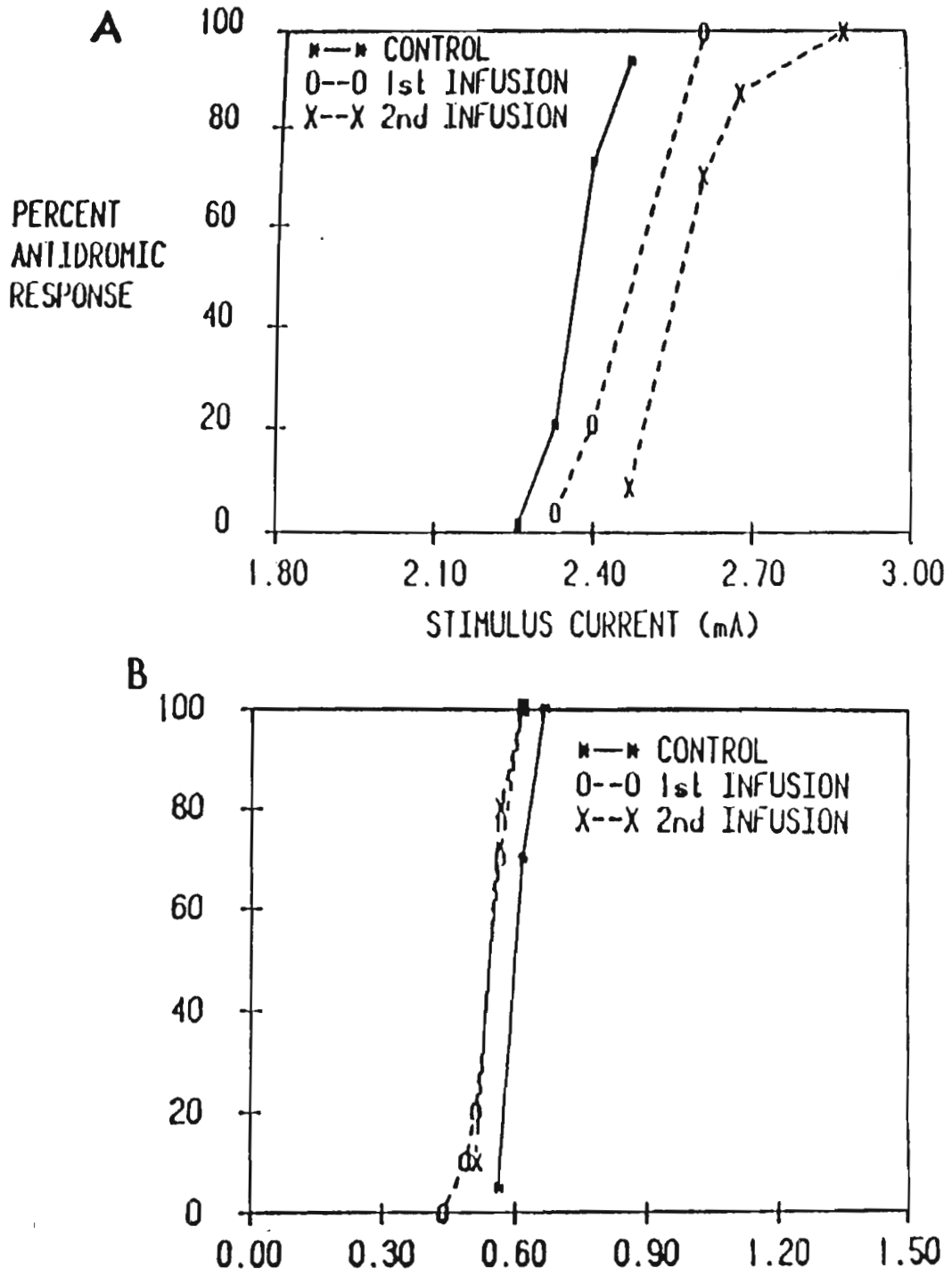


Fig. 3: A. Local infusion of d-amphetamine (10 μM, 300 nl) into neostriatal terminal fields of a dopaminergic neuron produces decreased terminal excitability. B. Identical infusion into neostriatum of a rat treated 18 and 3 hours prior to experiment with 250 mg/kg i.p. alpha-methyl-p-tyrosine demonstrates that depletion of endogenous dopamine eliminates the amphetamine effect.

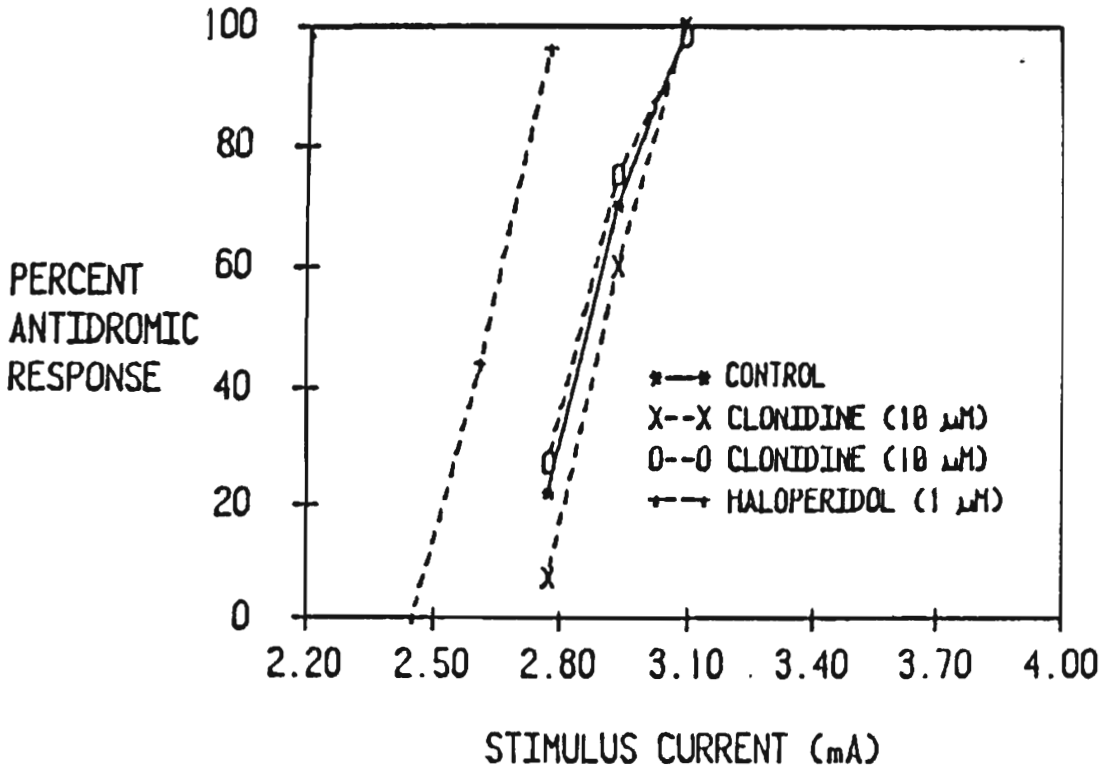


Fig. 4: Successive local infusions of the alpha-2 noradrenergic autoreceptor agonist, clonidine (10 μM, 300 nl) into terminal fields of a nigrostriatal dopamine neuron do not effect dopaminergic terminal excitability. The terminal is responsive, however, since a subsequent infusion of the dopamine autoreceptor antagonist, haloperidol (1 μM, 300 nl) produces a marked increase in terminal excitability.

5-HT_{1B} receptor (Martin and Sanders-Buch, 1982; Middlemiss, 1984; Engel et al., 1986). Interestingly, the terminal and soma-dendritic autoreceptors of serotonergic neurons appear to be pharmacologically distinct, since the latter resembles the $5HT_{1A}$ receptor subtype (Verge et al., 1985). This is in contrast to noradrenergic and dopaminergic neurons in which the nerve terminal autoreceptor appears to be pharmacologically similar or identical to the cell body autoreceptor that inhibits firing rate. Thus, although methiothepin is effective at serotonergic nerve terminals, it is an ineffectual antagonist at the cell body autoreceptor and, in fact, produces inhibition rather than facilitation of serotonergic neuronal activity when administered intravenously (Haigler and Aghajanian, 1977; unpublished observations).

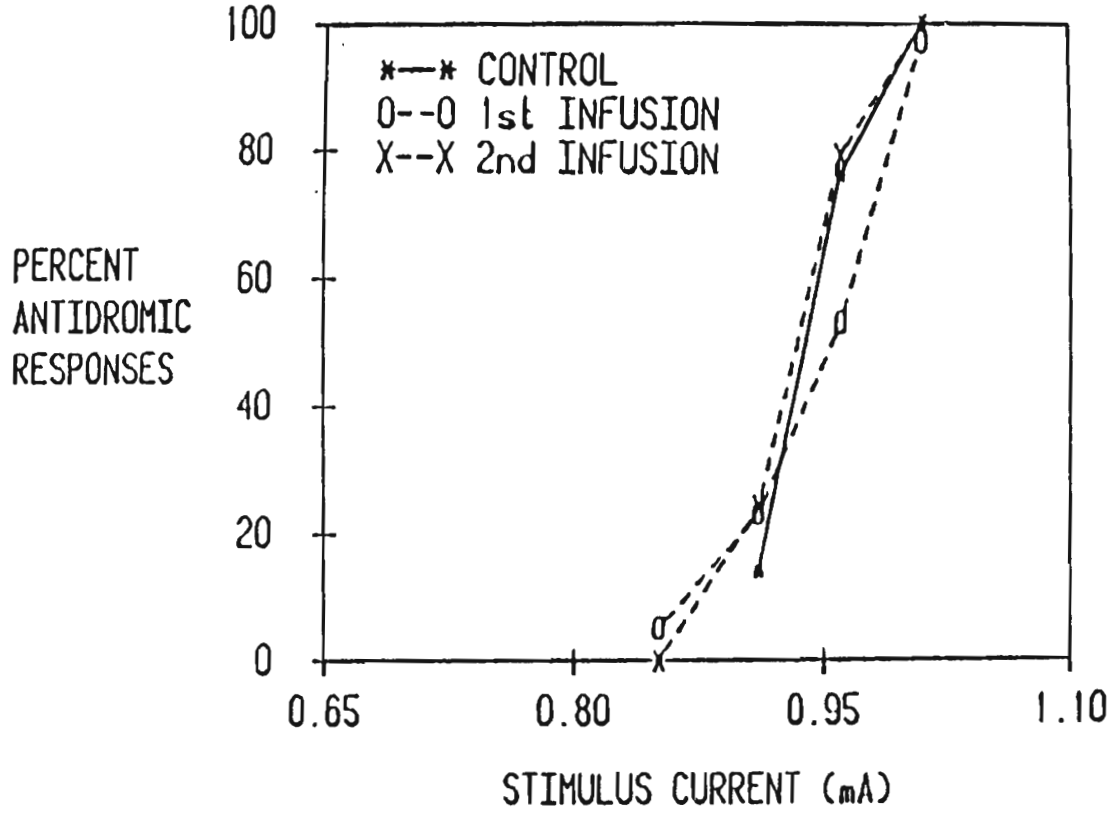


Fig. 5: Successive co-infusions of 5-MeODMT and the serotonergic terminal autoreceptor antagonist methiothepin (each at 10 μM) fail to alter neostriatal serotonergic terminal excitability, attesting to the specific, receptor-mediated nature of the effects of 5-MeODMT alone.

2.2 Amphetamine: Differences between Dopaminergic and Noradrenergic Neurons

In the preceding chapter we reported that the effects of amphetamine on locus coeruleus terminal excitability depend on the route of administration, producing decreases in noradrenergic terminal excitability when infused directly into the cortical terminal fields, but leading to increased terminal excitability when administered intravenously (Nakamura et al., 1982b; Ryan et al., 1985a). However, with DA neurons, amphetamine almost always leads to marked decreases in terminal excitability regardless of whether it is administered systemically or locally (Groves et al., 1981; Tepper et al., 1984a). This difference between dopaminergic and noradrenergic neurons in response to amphetamine derives from an indirect action of the effects of amphetamine at cell body and terminal autoreceptors. The ability of

amphetamine to increase extracellular concentrations of catecholamines has been shown to be dependent, at least in part, on ongoing impulse traffic (von Voigtlander and Moore, 1973). DA neurons are less sensitive to the firing-rate inhibiting effects of amphetamine than noradrenergic locus coeruleus neurons, when amphetamine is administered intravenously at modest doses (0.25-0.5 mg/kg). Therefore, dopaminergic neurons may maintain a sufficient firing rate to permit amphetamine to promote increased extracellular concentrations of DA at the terminal, and lead to increased autoreceptor stimulation (Groves and Tepper, 1983).

2.3 Effects of Autoreceptor Antagonists

DA autoreceptor antagonists exert effects on DA terminal excitability in the absence of exogenous DA agonists. It can be seen in Figure 4 that, even though repeated clonidine infusions did not alter terminal excitability, a subsequent infusion of haloperidol (1 μM) led to a marked increase in terminal excitability. Similar effects are obtained with local or intravenous administration of the DA autoreceptor antagonists fluphenazine or sulpiride. Analogous effects were obtained in serotonergic neurons following infusions of methiothepin into neostriatal terminal fields, as illustrated in Figure 6. These results indicate that, as in *in vitro* slice preparations, there are sufficient concentrations of endogenous monoamines in the terminal regions of dopaminergic and serotonergic neurons *in vivo* to maintain a tonic activation of the autoreceptors, and point to a physiological role of the autoreceptor in modulating monoamine release *in vivo* (Tepper et al., 1985).

This interpretation is strengthened by the observation that, in DA neurons, the magnitude of the drug-induced changes in terminal excitability is proportional to the firing rate of the neuron. Autoreceptor agonists produce large decreases in terminal excitability in slowly firing neurons, and exert more modest effects in rapidly firing neurons. The opposite relation obtains with respect to autoreceptor antagonists, where large increases in terminal excitability are observed in rapidly firing neurons and negligible effects are seen in slowly firing neurons (Tepper et al., 1984a). These relations are illustrated in Figure 7. (A similar relationship between pre-drug firing rate and the magnitude of the threshold changes following 5-MeODMT in serotonergic neurons was suggested, but failed to reach statistical significance (Sawyer et al., 1985).) This relationship suggests that the measurements of terminal excitability reflect the total amount of autoreceptor stimulation, that arising from endogenous agonist released as a function of ongoing impulse activity, and that arising from the administation of exogenous agonists. Thus, in a rapidly firing neuron, the extracellular concentration of neurotransmitter available for binding to the autoreceptor is high. Under these conditions, addition of exogenous agonists would exert relatively little effect since many

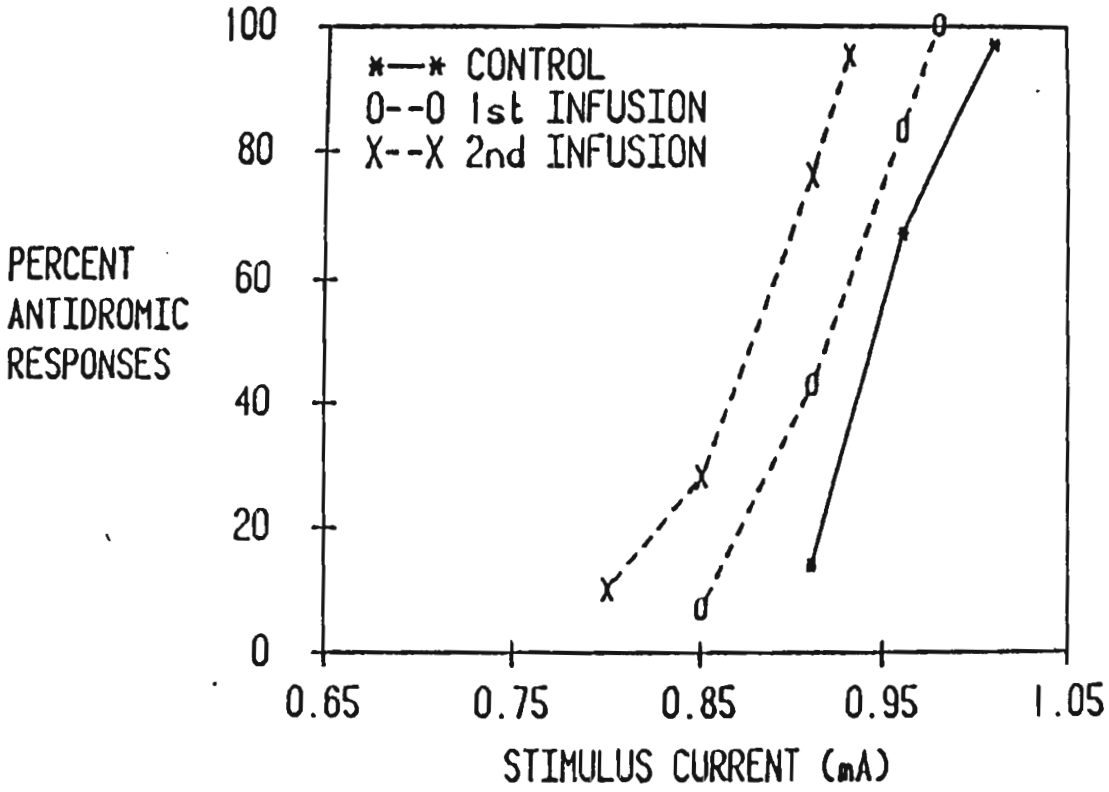


Fig. 6: Neostriatal infusion of methiothepin alone (10 μM, 300 nl) produces a dose-dependent increase in serotonergic terminal excitability.

or most of the autoreceptor sites would already be occupied by the endogenously released transmitter. Conversely, in slowly firing neurons where the amount of endogenous autoreceptor stimulation would be at a minimum, exogenous agonists could exert significant effects at the terminal by binding to the unoccupied autoreceptors, whereas antagonists could exert only a relatively weak effect. These data are in good agreement with biochemical release studies demonstrating that autoreceptor agonists are most effective at inhibiting DA release when release is evoked by low frequencies of electrical stimulation, and that antagonists are most effective at facilitating release when higher (but still physiologically relevant) frequencies of stimulation are employed (Cubeddu and Hoffmann, 1982; Hoffmann and Cubeddu, 1982; Lehmann and Langer, 1982; Cubeddu et al., 1983).

2.4 Effects of Increases in Impulse Flow

Autoreceptor-mediated changes in terminal excitability can also be demonstrated in dopaminergic neurons *in vivo* in the absence of exogenous

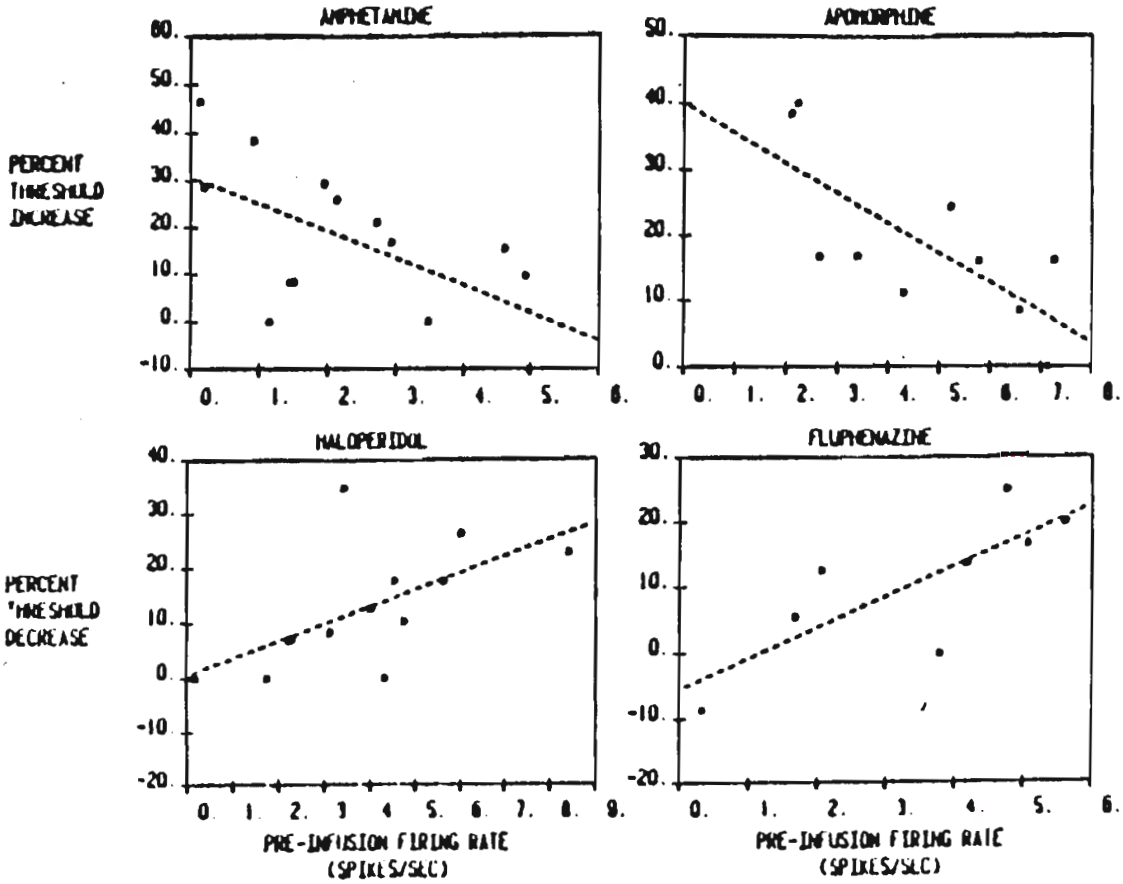


Fig. 7: Changes in threshold following striatal infusions of dopamine agonists and antagonists are correlated with pre-drug firing rates. Following infusions of 10 μM amphetamine or apomorphine, threshold increases are large in slowly firing cells and smaller in more rapidly firing neurons (AMP: $r = 0.61$, $df = 13$, $p < .06$, APO: $r = 0.73$, $df = 9$, $p < .05$). The opposite relation obtains following infusions of 1 μM haloperidol or 10 μM fluphenazine, where decreases in threshold (increases in excitability) are small in slowly firing neurons but large in more rapidly firing cells (HAL: $r = 0.66$, $df = 13$, $p <$ .06p; FLU: $r = 0.79$, $df = 7$, $p < .05$). The percent change in threshold stimulating current is shown on the ordinates and the pre-infusion firing rate is shown on the abcisses. (From Tepper et al., 1984a, with permission).

drug administration. Just as in noradrenergic neurons, the terminal excitability of dopaminergic neurons varies with firing rate in single substantia nigra or ventral tegmental area neurons (Tepper et al., 1984b; Tepper et al., 1987; Gariano et al., 1989). When the firing rate is high, terminal excitability is decreased, and vice versa. Furthermore, this relationship can be uncoupled in dopaminergic neurons by administration of haloperidol, suggesting that it derives from increased autoreceptor stimulation resulting from the higher extracellular concentrations of DA that occur during periods of increased impulse activity (Tepper et al., 1984b; Tepper et al., 1987). A similar phenomenon can be demonstrated by artificially increasing the rate of impulses reaching the terminal fields of dopaminergic neurons by stimulating pre-terminal regions of the axons in the MFB (Tepper et al., 1984b). Figure 8 illustrates this phenomenon for a dopaminergic nigrostriatal neuron. It can be seen that the stimulus current that is capable of provoking antidromic responses to each neostriatal stimulus in the absence of any conditioning stimulus to the MFB (A) becomes unable to elicit any response when delivered 225 ms after 750 ms trains of 5 pulses to the MFB (B). Complete recovery of pre-stimulus terminal excitability ensues after cessation of the conditioning pulses (C). After 0.1 μM haloperidol is infused into the striatal stimulating site, increased impulse flow no longer affects terminal excitability. This demonstrates that it is not the increased impulse flow *per se* that decreased terminal excitability, but rather the effects of the increased DA accumulation induced by the increased impulse flow acting on the terminal autoreceptors that is responsible for the decreased excitability.

Like the effects of exogenously applied autoreceptor agonists, the magnitude of the threshold increases following artificially increased rates of impulse traffic are inversely proportional to the baseline firing rate of the neuron under study. Furthermore, as with exogenous autoreceptor agonists, decreased excitability induced by increased impulse flow occurs only at the terminals, and not at more proximal regions of dopaminergic axons (Tepper et al., 1984b).

Reduced terminal excitability is observed *in vivo* under a variety of conditions that produce reduced release of transmitter per pulse in *in vitro* experiments. The data reviewed above and in the preceding chapter demonstrate that dopaminergic and noradrenergic terminal excitability are reduced at high rates of impulse traffic. Thus, one physiologically relevant effect of terminal autoreceptors may be to reduce the amount of transmitter released by each presynaptic impulse at sustained high rates of firing. Indeed, reduced release per pulse has been measured *in vitro* for DA release elicited by sustained high, but still physiologically relevant, stimulus frequencies (Cubeddu and Hoffmann, 1982; Cubeddu et al., 1983). A similar relation obtains for norepinephrine and acetylcholine release per pulse and stimulation frequency (Mayer et al., 1988). This property may have special significance to

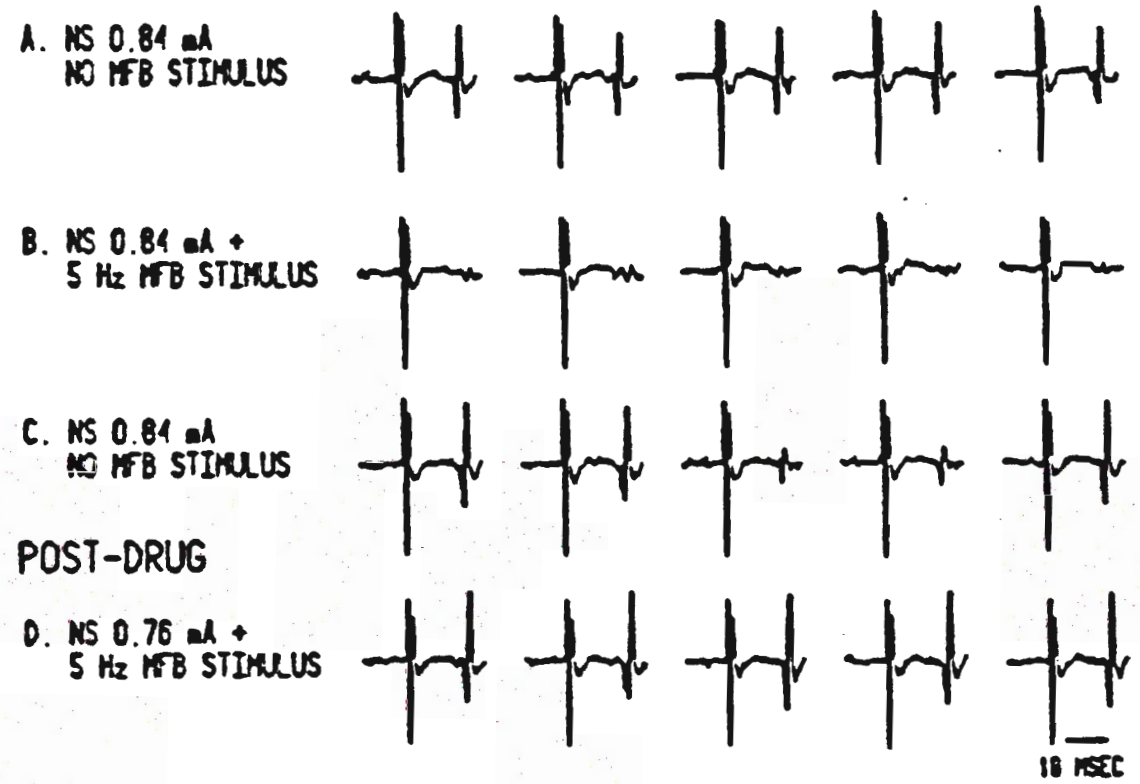


Fig. 8: Effects of stimulus-induced alterations in the rate of impulse traffic on dopaminergic terminal excitability. A. Prior to the MFB conditioning 0.84 mA is at threshold and produces an antidromic response to each stimulus. B. When the same stimulus is applied 225 ms following a 5 Hz train of pulses to the MFB, antidromic responding is abolished due to increased threshold. C. When the MFB conditioning is stopped, excitability returns to pre-stimulation levels and antidromic responding to each stimulus is restored. D. After local infusion of haloperidol into the neostriatal stimulating site, the threshold current is lowered slightly as the terminal excitability is increased, and the effects of MFB conditioning at 5 Hz are completely blocked. (From Tepper et al., 1985, with permission).

dopaminergic neurotransmission, since dopaminergic neurons are known to fire a proportion of their spikes in bursts (Grace and Bunney, 1984), and the temporal characteristics of the MFB stimuli used to manipulate firing rate closely match those of the endogenous bursts.

Although serotonergic neurons did respond to increases in impulse flow with decreased terminal excitability, it is noteworthy that serotonergic neurons seemed less sensitive to the effects of impulse flow than did dopaminergic or noradrenergic neurons. Whereas the excitability of dopaminergic neurons could be transiently decreased by 30-40% by 10 Hz MFB conditioning stimulation, a similar increase in impulse flow along serotonergic axons evoked only a 5-15% decrease in terminal excitability. A possible explanation for this quantitative difference is discussed in a later section of this chapter.

3. MORPHOLOGICAL CONSIDERATIONS

Although there is now good evidence to support the view that terminal autoreceptors do play an active role in modulating monoamine release *in vivo*, the anatomical basis for the observed effects is still unclear. The physical location of the autoreceptor modulating DA release has not been unequivocally demonstrated with biochemical release studies. It has been argued that, since tetrodotoxin fails to block the autoinhibition, postsynaptic neurons are not involved and thus the autoreceptor must be located presynaptically (Jackisch et al., 1980). However, blockade of sodium channels only rules out the participation of sodium action potentials in postsynaptic neurons, leaving electrotonic interactions or calcium-mediated action potentials as possibilities. A more convincing demonstration of the presynaptic location of the autoreceptor and lack of involvment of postsynaptic neurons in autoinhibition is the fact that local injection of kainic acid into the neostriatum, which selectively destroys striatal neuronal cell bodies and their processes but leaves axons of passage intact, does not affect DA autoreceptor-mediated changes in terminal excitability, as shown in Figure 9.

Even though we can now localize the autoreceptor to the presynaptic axon, the source of the endogenous autoreceptor agonist remains uncertain. In the striatum, for example, although a close apposition of dopaminergic terminals has been observed infrequently, neither membrane specializations nor accumulation of synaptic vesicles indicative of true axo-axonic contact were found (Pickel et al., 1981). Other studies employing analysis of serial thin sections of dopaminergic and non-dopaminergic axonal profiles have also failed to find evidence for the existence of axo-axonic synapses in rat neostriatum (Groves, 1980; Freund et al., 1984; Bouyer et al., 1984a; Bouyer et al., 1984b). Thus, it is likely that the *in vivo* activation of dopaminergic

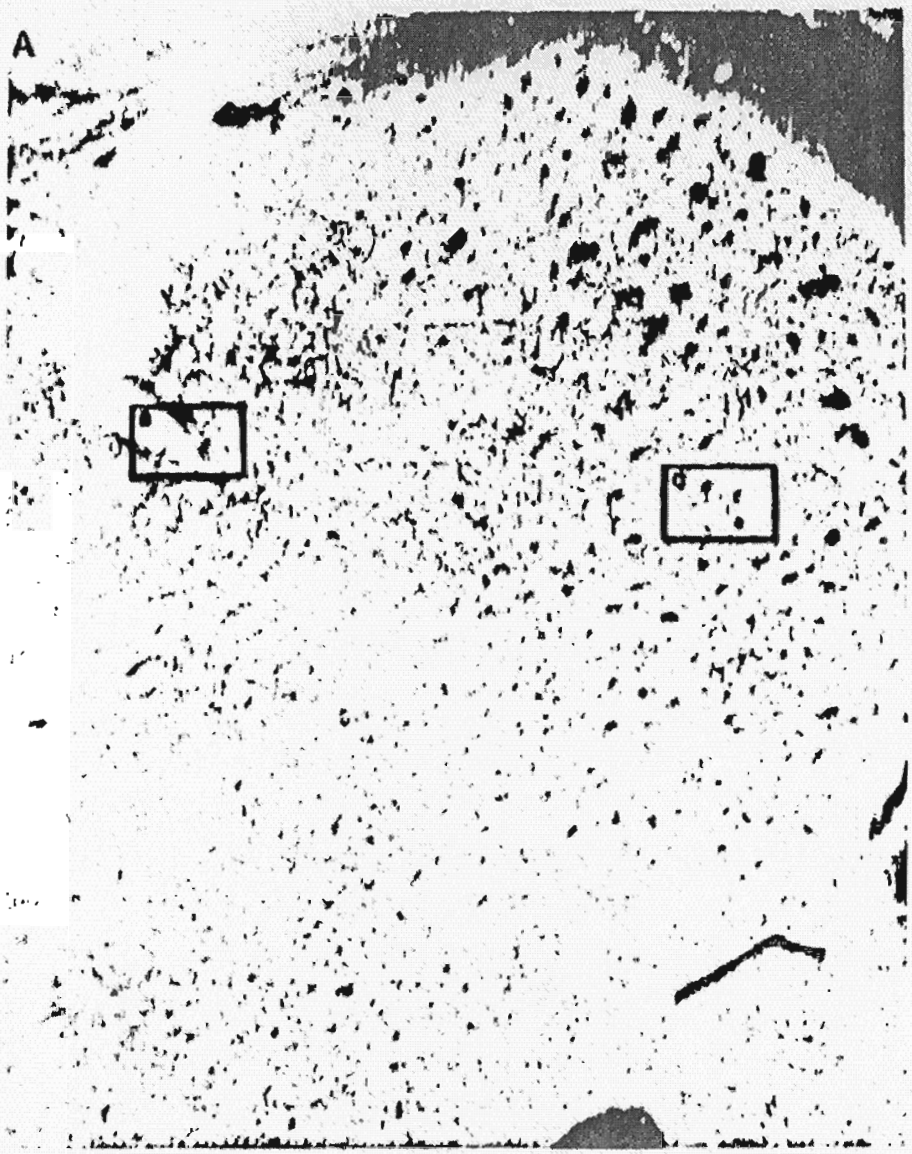
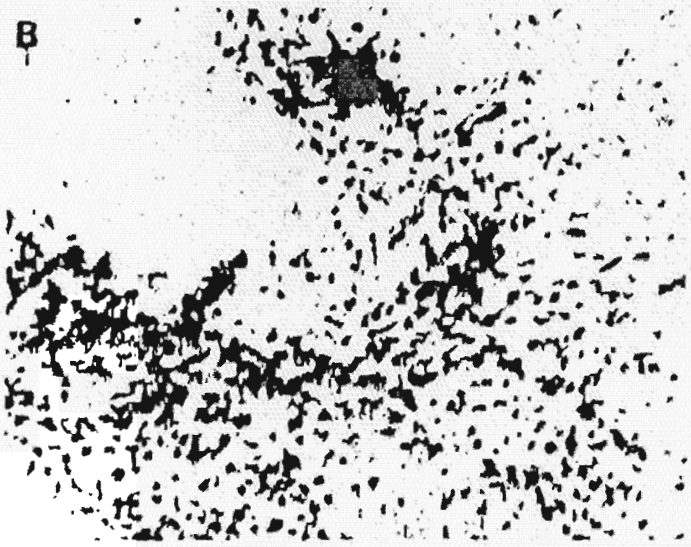
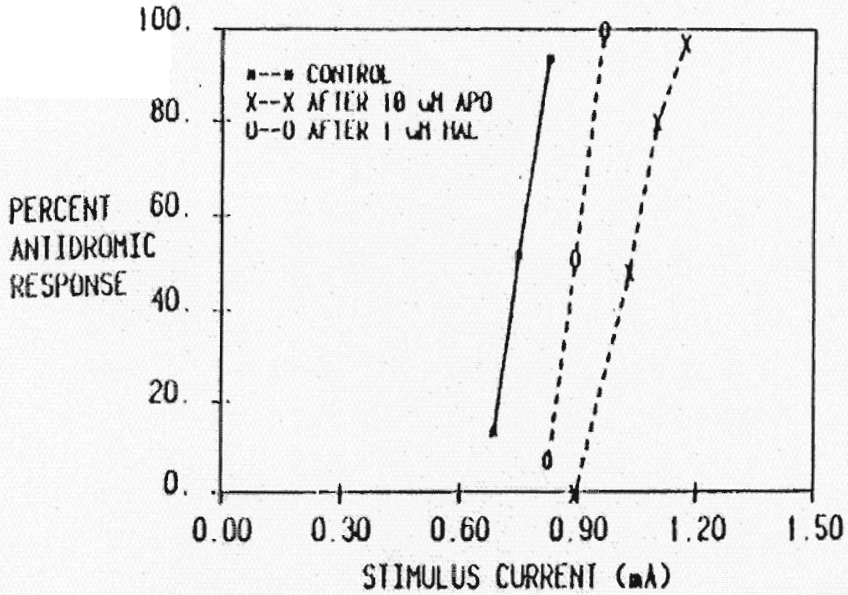


Fig. 9: A. Low magnification micrograph of neostriatum 7 days after local injection of kainic acid 1.25 μg/μl, 0.5 μl. The large lesion at the top left was made by the cannula from the kainate injection and the subsequent placement, 7 days later, of the stimulation/infusion apparatus. B. higher magnification view of the area marked B in A. There is extensive glial profusion and a total absence of postsynaptic neostriatal neurons; otherwise, the neuropil and fiber fascicles appear grossly normal. C. Relatively unaffected portion of striatum marked C in A for comparison with B. D. Effects of local infusion of apomorphine into the site marked B. Apomorphine (10 μM, 300 nl) produced its typical decrease in terminal excitability that was partially reversed by a subsequent infusion of haloperidol (0.31 ul, 1 μM) through a second cannula. (From Tepper et al., 1987, with permission.)


B


C


100.
80.
60.
40.
20.
0.
PERCENT ANTIDROMIC RESPONSE
--- CONTROL
X--X AFTER 10 uM APO
0--0 AFTER 1 uM HAL
0.00
0.30
0.60
0.90
1.20
1.50
STIMULUS CURRENT (mA)

and serotonergic autoreceptors in neostriatum does not result from true axo-axonic synaptic contact onto the autoreceptor, but rather could result from the diffusion of synaptically released neurotransmitter away from its postsynaptic target (Groves, 1980).

Results from recent *in vivo* voltammetric studies of DA release in striatum indicate that 1 second electrical stimulation of the MFB produces extracellular DA levels in the micromolar range, and calculations indicate that the released DA diffuses some 5-20 μm before reaching the site of voltammetric measurement (Kuhr and Wightman, 1986; Stamford et al., 1986). Thus, under *in vivo* conditions, DA release in the striatum is at concentrations equivalent to those of the exogenous agonists employed in the terminal excitability experiments. Furthermore, the extent of diffusion calculated in the voltammetric studies is more than sufficient to account for the autoreceptor-mediated effects on terminal excitability and transmitter release without the necessity of assuming synaptic contact between adjacent axon terminals or boutons *en passant*. Although axo-axonic synapses are known to exist in cerebral cortex, the frequency of their occurrence compared to the ubiquity of monoamine terminals (Olschowka et al., 1981) suggests that, as with striatal dopaminergic autoreceptors, activation of cortical monoaminergic autoreceptors *in situ* probably occurs by way of diffusion, and not through the action of axo-axonic synapses. From a functional point of view, it makes more sense for a system that apparently functions as a local negative feedback mechanism for controlling neurotransmitter concentration in a given region to be directly responsive to extracellular concentrations of neurotransmitter in that region rather than depending on a specific axo-axonic synaptic input arising from a distant neuron. Moreover, the latter might not reflect the true situation at the synapse being modulated.

4. MECHANISMS OF AUTOINHIBITION

4.1 Interpretation of Changes in Terminal Excitability

Decreased excitability of neuronal structures has long been associated with membrane hyperpolarization, and increased excitability with membrane depolarization (Wall, 1958; Hubbard et al., 1969). Intra-axonal recordings while testing excitability from central nervous system axons are consistent with this interpretation (Kocsis and Waxman, 1982). Direct depolarization of noradrenergic or dopaminergic terminals by local infusion of potassium leads to marked increases in noradrenergic and dopaminergic terminal excitability, consistent with the interpretation that autoreceptor-mediated decreases in terminal excitability reflect a terminal hyperpolarization while the increased

excitability resulting from autoreceptor antagonists reflects a depolarization of the terminals (Groves et al., 1981; Nakamura et al., 1981; Tepper et al., 1984a). Recent *in vitro* intracellular recordings from cell bodies of noradrenergic, dopaminergic and serotonergic neurons have revealed that stimulation of autoreceptors in each case, as well as stimulation of soma-dendritic opiate receptors on locus coeruleus neurons, produces a hyperpolarization associated with an increase in conductance to potassium (Williams et al., 1985; Aghajanian and Lakoski, 1984; Lacey et al., 1987; Lacey et al., 1988). Under certain conditions a net increase in membrane conductance could also raise threshold and decrease excitability (Hubbard et al., 1969). However, the brief duration of the antidromic test pulses and other aspects of the excitability testing paradigm strongly suggest that what is being indexed by measuring changes in terminal excitability is the resting membrane potential of the presynaptic terminal regions. Thus, in central monoaminergic neurons, autoreceptor-mediated inhibition of transmitter release occurs when terminals are hyperpolarized, probably due to an increase in conductance to potassium.

4.2 Impulse Conduction Failure in Central Monoamine Neurons?

But how does a terminal hyperpolarization and conductance increase lead to inhibition of release? In the peripheral nervous system, there is good evidence that stimulation of autoreceptors and presynaptic opiate receptors produces inhibition of NE release at least in part by impeding conduction of the action potential down the axon, leading to impulse failure proximal to some of the sites of transmitter release (Stjarne, 1978; Alberts et al., 1981; Morita and North, 1981; see also Stjarne, this volume). Indeed, some of the evidence from the terminal excitability experiments reviewed above is consistent with alterations in electrical properties that could affect impulse conduction along the axon. However, conduction failure as described for peripheral autonomic neurons most likely cannot account for monoamine autoreceptor effects in the central nervous system since, when autoreceptor stimulation produces a decreased frequency of antidromic responding, it is always possible to obtain antidromic responding on 100% of the stimulus trials by increasing the stimulus strength at the terminals. Thus, there cannot be failure of the antidromic impulse at any point between the site of impulse initiation and site of recording at the cell body. Furthermore, when antidromic thresholds are raised by autoreceptor stimulation, antidromic latencies are slightly prolonged, and their variability is slightly increased (Nakamura et al., 1981; Tepper et al., 1984a). These observations suggest that the antidromic response has traversed a region of the axon that is hyperpolarized or possesses increased conductance. Since most of the sites of

transmitter release on central monoamine axons occur *en passant*, if impulse failure does occur with autoreceptor stimulation, it must happen only at relatively infrequent terminal boutons, or at branch points in the finest terminal twigs. Since autoreceptor stimulation can inhibit evoked release by such a substantial amount, it seems unlikely that conduction failure limited to these sites could account for the effect. For a more detailed discussion of the role of impulse conduction failure in central autoinhibition, see Ryan et al. (1985b).

4.3 The Role of Potassium and Calcium Conductances

It is far more likely that some change in depolarization-release coupling accounts for autoreceptor-mediated inhibition of transmitter release. Since it is well established that calcium influx and utilization are the critical events in exocytotic transmitter release (Llinas et al., 1976; Zucker and Lando, 1986), it is likely that some aspect of calcium entry and/or utilization is affected by autoreceptor stimulation. Thus, when DA release is elicited by calcium-independent stimuli (e.g., amphetamine or tyramine), such release is not affected by autoreceptor stimulation (Kamal et al., 1981). In synaptosomal preparations of cortex, norepinephrine release can be evoked by the addition of the calcium ionophore, A23187. However, unlike release elicited by electrical or potassium-induced depolarization, NE release evoked by A23187, which bypasses the voltage-dependent calcium conductance at the terminals, is not subject to modification by presynaptic autoreceptors (DeLangen and Mulder, 1980). A considerable body of electrophysiological evidence from North, Williams and associates now exists that suggests that, at least as far as noradrenergic locus coeruleus neurons are concerned, there is indeed an action of presynaptic receptors on inward calcium currents, and that this effect is indirect, mediated by a potassium-dependent hyperpolarization (North and Williams, 1983; Williams and North, 1984, 1985; Bug et al., 1986).

In vitro intracellular recordings from locus coeruleus neurons reveal that stimulation of noradrenergic autoreceptors or opiate receptors on the soma-dendrite leads to a hyperpolarization that is mediated by an increase in conductance to potassium (North and Williams, 1983, 1985; Williams et al., 1985). Stimulation of these soma-dendritic receptors has also been shown to inhibit calcium action potentials in locus coeruleus neurons (North and Williams, 1983; Williams and North, 1985). Although these investigators could demonstrate a direct inhibition of the calcium action potential by autoreceptor or opiate agonists under conditions in which the potassium conductance had been blocked, this effect required agonist concentrations several orders of magnitude higher than those required to demonstrate inhibition of the calcium action potential when the autoreceptor-mediated

potassium conductance increase was not blocked. Thus, although there is some evidence for a direct effect of noradrenergic autoreceptor agonists on calcium conductance, the results of Williams, North and associates suggest that NE release is inhibited overall by autoreceptor stimulation "because the membrane potassium conductance is increased" (Williams and North, 1985). Furthermore, both opiate receptors and autoreceptors at the soma-dendritic region of locus coeruleus neurons appear to be linked to the same set of potassium channels (North and Williams, 1985). Thus, it appears that the mechanism underlying both terminal autoreceptor and presynaptic opiate receptor-mediated inhibition of NE release is the same, and involves a decrease in calcium entry brought about by an increase in conductance to potassium.

Attempts to directly demonstrate the involvement of a potassium conductance increase in autoreceptor mediated decreases in dopaminergic terminal excitability *in vivo* with 4-aminopyridine (4-AP, 0.1 -1 mM) or tetraethylammonium (TEA, 0.1 mM) were unsuccessful (Tepper et al., 1986). In fact, both 4-AP and TEA alone produced decreased terminal excitability that was shown to be a consequence of increased dopamine release. However, more recent *in vitro* studies have demonstrated that the D_2 somatodendritic autoreceptor-mediated hyperpolarization in nigral slices can indeed be blocked by TEA, but only at concentrations 2-3 orders of magnitude (10-100 mM) greater than those employed in the terminal excitability experiments (Lacey et al., 1987). At lower concentrations, TEA produced results analogous to those obtained in the terminal excitability studies, i.e., an increase in the inward current that is consistent with increased dendritic release of dopamine acting locally on somadendritic autoreceptors. Thus it would appear that there are at least 2 populations of potassium channels at the terminals and somadendritic regions of dopaminergic neurons. One is presumably principally voltage dependent, displays great sensitivity to TEA, but does not directly affect autoreceptor operation. Blockade of this channel leads to increased dopamine release from both terminals and dendrites of dopaminergic neurons. The other is neurotransmitter (i.e., DA) dependent and relatively insensitive to TEA, and is the channel that mediates the autoreceptor-mediated increase in potassium conductance.

4.4 Autoreceptor-Mediated Changes in Terminal Excitability: Differences Between Noradrenergic, Dopaminergic and Serotonergic Neurons and the Possible Mechanisms Involved

Although there was a marked qualitative similarity among noradrenergic, dopaminergic and serotonergic neurons in autoreceptor-mediated changes in terminal excitability, it was consistently noted that serotonergic neurons

exhibited drug- or impulse-related decreases in terminal excitability that were approximately one-half the magnitude of analogous changes in noradrenergic or dopaminergic terminal excitability. Several possible explanations for these differnces exist. It is possible that the density of terminal autoreceptors differs among the monoamine neurons, with 5-HT terminals possessing the lowest density. This is unlikely, however, since the *in vitro* release studies indicate that the maximal autoreceptor-mediated inhibition of release is equivalent for the three types of terminals.

Firing rate could also play a role in the apparent differential sensitivity, for the reasons discussed earlier. Of the three monoamine neuron types studied, serotonergic neurons were the slowest firing, which would tend to make them most sensitive to administration of exogenous agonists or increases in impulse flow, not the least sensitive.

A more likely explanation involves ionic mechanisms. Since the autoreceptor-mediated hyperpolarization at monoamine terminals probably occurs due to an increase in potassium conductance, its magnitude depends on the distribution of potassium ions across the terminal membrane which determines the potassium equilibrium potential (E_k). A decrease in the E_k in serotonergic terminals relative to noradrenergic or dopaminergic terminals would result in a smaller hyperpolarization for an equal increase in potassium conductance. Thus, although admittedly speculative, the possibility exists that the relatively smaller autoreceptor-mediated changes in terminal excitability of serotonergic neurons compared to noradrenergic and dopaminergic neurons reflects a smaller terminal hyperpolarization, perhaps as a function of a less negative E_k in serotonergic terminals. Since the actual inhibition of release is probably more a function of the conductance change than a membrane potential change, e.g., Baxter and Bittner, 1981, a slightly less negative E_k would not be expected to counteract the inhibition of release, although it would decrease the hyperpolarization, and hence the magnitude of the change in excitability.

5. CONCLUSIONS

The experimental results summarized in this and the preceding chapter point toward a general similarity among central noradrenergic, dopaminergic and serotonergic neurons with respect to the neuronal events underlying both autoreceptor- and other presynaptic receptor-mediated modifications of evoked transmitter release. In all cases, pharmacological stimulation of the autoreceptor leads to marked decreases in the electrical excitability of the terminal regions *in vivo*, probably reflecting a terminal hyperpolarization (Groves et al., 1981; Nakamura et al., 1981, 1982b; Tepper et al., 1984a,b; Sawyer et al., 1985; Ryan et al., 1985a; Mereu et al., 1985; Gariano et al.,

1989). (However, not all *presynaptic* monoamine receptors have this effect; for example, presynaptic DA receptors on non-dopaminergic hippocampal terminals mediate increases in terminal excitability [Yang and Mogenson, 1986].) In noradrenergic neurons, stimulation of presynaptic opiate receptors also leads to decreased terminal excitability *in vivo* (Nakamura et al., 1982a). As reviewed elsewhere in this volume, these same pharmacological manipulations lead, *in vitro*, to inhibition of evoked transmitter release. Hence, autoreceptor and presynaptic opiate receptor-mediated inhibition of transmitter release occurs under conditions of decreased terminal excitability. Furthermore, evidence from slice preparations suggests additional similarities with respect to autoreceptor effects in central noradrenergic, dopaminergic and serotonergic neurons, since in all these neurons the effect of stimulation of the soma-dendritic autoreceptor is a hyperpolarization mediated by an increase in conductance to potassium (Williams et al., 1985; Aghajanian and Lakoski, 1984; Lacey et al., 1987; 1988). It is likely that the three terminal autoreceptor types share this property.

Thus, it seems probable that the autoreceptor-mediated changes in terminal excitability and transmitter release in the three types of central monoamine neurons all reflect the same phenomenon. Autoreceptor stimulation leads to an increase in potassium conductance and an accompanying hyperpolarization that acts to decrease the size and/or duration of the presynaptic calcium spike that triggers the exocytotic release of neurotransmitter. The evidence reviewed in this and the preceding chapter also suggests that terminal autoreceptors play a significant role in the endogenous modulation of monoaminergic synaptic transmission *in vivo*.

ACKNOWLEDGEMENTS

We are grateful to Dr. S.J. Young for valuable suggestions during many of the experiments reviewed in this chapter. We than Ms. Elizabeth K. Wilson for assistance with the preparation of the figures. Some of the research reviewed and the writing of this manuscript were supported by the National Institute on Drug Abuse Grant DA-02854 and Research Scientist Award DA-00079 to PMG, and by the National Institute of Mental Health Grant MH45286 to JMT.

REFERENCES

Aghajanian GK and Bunney BS. Dopamine 'autoreceptors': Pharmacological characterization by microiontophoretic single cell recording studies. Nauyun-Schmiedeberg's Arch Pharmacol 197: 1-7 (1977).

Aghajanian GK and Lakoski JM. Hyperpolarization of serotonergic neurons by serotonin and LSD: Studies in brain slices showing increased K^+ conductance. Brain Res 305: 181-185 (1984).

Aghajanian GK and Vandermaelen CP. Alpha-adrenoceptor-mediated hyperpolarization of locus coeruleus neurons: Intracellular studies in vivo. Science 215: 1394-1396 (1982).

Alberts P, Bartfai T and Stjarne L. Site(s) and mechanisms of autoinhibition and facilitation of [^{3}H]noradrenaline secretion in guinea pig vas deferens. J Physiol (Lond) 312: 297-334 (1981).

Baumann PA and Waldmeier PC. Further evidence for negative feedback control of serotonin release in the central nervous system. Naunyn-Schmiedeberg's Arch Pharmacol 317: 36-43 (1981).

Baxter DA and Bittner GD. Intracellular recordings from crustacean motor axons during presynaptic inhibition. Brain Res 223: 422-428 (1981).

Bouyer JJ, Miller RJ and Pickel VM. Ultrastructural relation between cortical efferents and terminals containing enkephalin-like immunoreactivity in rat neostriatum. Regulat Peptides 8: 105-115 (1984a).

Bouyer JJ, Park DH, Joh TH and Pickel VM. Chemical and structural analysis of the relation between cortical inputs and tyrosine hydroxylase-containing terminals in rat neostriatum. Brain Res 302: 267-275 (1984b).

Boyar WC and Altar CA. Modulation of in vivo dopamine release by D_2 but not D_1 receptor agonists and antagonists. J. Neurochem 48: 824-831 (1987).

Bug W, Williams JT and North RA. Membrane potential measured during potassium-evoked release of noradrenaline from rat brain neurons: Effects of normorphine. J Neurochem 47: 652-655 (1986).

Chesselet M-F. Presynaptic regulation of neurotransmitter release in the brain: Facts and hypothesis. Neurosci 12: 347-375 (1984).

Cubeddu LX and Hoffmann IS. Operational characteristics of the inhibitory feedback mechanisms for regulation of dopamine release via presynaptic receptors. J Pharmacol Exp Therapeut 223: 497-501 (1982).

Cubeddu LX, Hoffmann IS and James MK. Frequency-dependent effects of neuronal uptake inhibitors on the autoreceptor-mediated modulation of dopamine and acetylcholine release from the rabbit striatum. J Pharmacol Exp Therapeut 226: 88-94 (1983).

DeLangen CDJ and Mulder AH. On the role of calcium ions in the presynaptic alpha-receptor-mediated inhibition of ^{3}H-noradrenaline release from rat brain cortex synaptosomes. Brain Res 1985: 399-408 (1980).

Engel G, Gothert M, Muller-Schweinitzer E, Schlicker E, Slatonen L and Stadler PA. Evidence for common pharmacological properties of [^{3}H]5-hydroxytryptamine binding sites, presynaptic 5-hydroxytryptamine autoreceptors in CNS and inhibitory presynaptic 5-hydroxytryptamine receptors on sympathetic nerves. Naunyn-Schmiedeberg's Arch Pharmacol 332: 1-7 (1986).

Farnebo L-O and Hamberger B. Drug-induced changes in the release of ^3H monoamines from field-stimulated rat brain slices. Acta Physiol Scand (suppl) 371: 35-44 (1971).

Freund TF, Powell JF and Smith AD. Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. Neurosci 13: 1189-1215 (1984).

Gariano RF, Sawyer SF, Tepper JM, Young SJ and Groves PM. Mesocortical dopaminergic neurons. 2. Consequences of terminal autoreceptor activation. Brain Res Bull 22: 517-523 (1989).

Gothert M. Serotonin-receptor-mediated modulation of Ca^{2+}-dependent 5-hydroxytryptamine release from neurons of the rat brain cortex. Naunyn-Schmiedeberg's Arch Pharmacol 314: 223-230 (1980).

Gothert M and Wenheimer G. Extracellular 5-hydroxytryptamine inhibits 5-hydroxytryptamine release from rat brain cortex slices. Naunyn-Schmiedeberg's Arch Pharmacol 310: 93-96 (1979).

Groves PM. Synaptic endings and their postsynaptic targets in neostriatum: Synaptic specializations revealed from analysis of serial sections. Proc Natl Acad Sci 77: 6926-6929 (1980).

Groves PM, Fenster GA, Tepper JM, Nakamura S and Young SJ. Changes in dopaminergic terminal excitability induced by amphetamine and haloperidol. Brain Res 221: 425-431 (1981).

Groves PM and Tepper JM. Neuronal mechanisms of action of amphetamine. In: Creese I, ed. pp. 81-129, Stimulants: Neurochemical, Behavioral and Clinical Perspectives. New York: Raven Press, 1983.

Haigler HJ and Aghajanian GK. Serotonin receptors in the brain. Fed Proc 36: 2159-2164 (1977).

Helmreich I, Reimann W, Hertting G and Starke K. Are presynaptic dopamine autoreceptors and postsynaptic dopamine receptors in the rabbit caudate nucleus pharmacologically different? Neurosci 7: 1559-1566 (1982).

Hoffmann IS and Cubeddu LX. Rate and duration of stimulation determine presynaptic effects of haloperidol on dopaminegic neurons. J Neurochem 39: 585-588 (1982).

Hubbard JI, Llinas R and Quastal DMJ. Electrophysiological Analysis of Synaptic Transmission. Baltimore: Williams and Wilkins Co., pp. 15-84, 112-173, 1986.

Jackisch R, Zumstein A, Hertting B and Starke K. Interneurones are probably not involved in the presynaptic dopaminergic control of dopamine release in rabbit caudate nucleus. Naunyn-Schmiedeberg's Arch Pharmacol 314: 1129-1133 (1980).

Kamal LA, Arbilla S and Langer SZ. Presynaptic modulation of the release of dopamine from the rabbit caudate nucleus: Differences between electrical stimulation, amphetamine and tyramine. J Pharmacol Exp Therapeut 216: 592-598 (1981).

Kocsis JD and Waxman SG. Intra-axonal recordings in rat dorsal column axons: Membrane hyperpolarization and decreased excitability precede the primary afferent depolarization. Brain Res 238: 222-227 (1982).

Kuhr WG and Wightman RM. Real-time measurement of dopamine release in rat brain. Brain Res 381: 168-171 (1986).

Kuhr WG and Wightman RM. Real-time measurement of dopamine release in rat brain. Brain Res 381: 168-171 (1986).

Lacey MG, Mercuri NB and North RA. Dopamine acts on D_2 receptors to increase potassium conductance in neurons of the rat substantia nigra zona compacta. J Physiol (Lond) 392: 497-416 (1987).

Lacey MG, Mercuri NB and North RA. On the potassium conductance increased by $GABA_B$ and Dopamine D_2 receptors in rat substantia nigra. J Physiol (Lond) 401: 437-453 (1988).

Langer SZ. Presynaptic receptors and their role in the regulation of transmitter release. Br J Pharmacol 60: 481-497 (1977).

Langer SZ and Moret C. Citalopram antagonizes the stimulation by lysergic acid diethylamide of presynaptic inhibitory serotonin autoreceptors in the rat hypothalamus. J Pharmacol Exp Therapeut 222: 220-226 (1982).

Lehmann J and Langer SZ. The pharmacological distinction between central pre- and post-synaptic dopamine receptors: Implications for the pathology and therapy of schizophrenia. In: Kohsaka M, Shohmori T, Tsukada Y and Woodruuf GL, eds. Advances in Dopamine Research; Advances in Biosciences, Vol. 37, pp. 25-30. Oxford: Pergamon Press, 1982.

Llinas R, Steinberg IZ and Walton K. Presynaptic calcium currents and their relation to synaptic transmission: Voltage clamp study in squid giant synapse and theoretical model for the calcium gate. Proc Natl Acad Sci 73: 2918-2922 (1976).

Martin LL and Sanders-Busch E. Comparison of the pharmacological characteristics of $5HT_1$ and $5HT_2$ binding sites with those of serotonin autoreceptors which modulate serotonin release. Naunyn-Schmiedeberg's Arch Pharmacol 321: 165-170 (1982).

Mayer A, Limberger N and Starke K. Transmitter release patterns of noradrenergic, dopaminergic and cholinergic axons in rabbit brain slices during short pulse trains and the operation of presynaptic autoreceptors. Naunyn-Schmiedeberg's Arch Pharmacol 338: 632-643 (1988).

Mereu G, Westfall TC and Wang RY. Modulation of terminal excitability of mesolimbic dopaminergic neurons by D-amphetamine and haloperidol. Brain Res 359: 88-96 (1985).

Middlemiss DN. 8-Hydroxy-2-(di-n-propylamino) tetralin is devoid of activity at the 5-hydroxytryptamine autoreceptor in rat brain. Implications for the proposed link between the autoreceptor and the [^{3}H]5-HT recognition site. Naunyn-Schmiedeberg's Arch Pharmacol 327: 18-22 (1984).

Moret C. Pharmacology of the serotonin autoreceptor. In: Green AR, ed. Neuropharmacology of Serotonin, pp. 21-49. New York: Oxford University Press, 1982.

Morita K and North RA. Opiates and enkephalin reduces excitability of neuronal processes. Neurosci 6: 1943-1951 (1981).

Nakamura S, Tepper JM, Young SJ and Groves PM. Neurophysiological consequences of presynaptic receptor activation: Changes in noradrenergic terminal excitability. Brain Res 226: 155-170 (1981).

Nakamura S, Tepper JM, Young SJ, Ling N and Groves PM. Noradrenergic terminal excitability: Effects of opioids. Neurosci Lett 30: 57-62 (1982a).

Nakamura S, Tepper JM and Groves PM. Noradrenergic terminal excitability: Effects of presynaptic receptor stimulation and blockade. In: Feigenbaum JJ, Hanani M, eds. The Presynaptic Regulation of Neurotransmitter Release. London, Tel Aviv: Freund, 1989.

Nakamura S, Tepper JM, Young SJ and Groves PM. Changes in noradrenergic terminal excitability induced by amphetamine and their relation to impulse traffic. Neurosci 7: 2217-2224 (1982b).

North RA and Williams JT. Opiate activation of potassium conductance inhibits calcium action potentials in rat locus coeruleus neurons. Br J Pharmacol 80: 225-228 (1983).

North RA and Williams JT. On the potassium conductance increased by opioids in rat locus coeruleus neurones. J Physiol (Lond) 364: 265-280 (1985).

Olschowka JA, Molliver ME, Grzanna R, Rice FL and Coyle JT. Ultrastructural demonstration of noradrenergic synapses in the rat central nervous system by dopamine B-hydroxylase immunocytochemistry. J Histochem Cytochem 29: 271-280 (1981).

Pickel VM, Beckley SC, Joh TH and Reis DJ. Ultrastructural immunocytochemical localization of tyrosine hydroxylase in the neostriatum. Brain Res 225: 373-385 (1981).

Pickler L, Pifl C, Hornyiciewicz D and Kobinger J. The dopamine autoreceptor agonist B-HT 920 inhibits *in vivo* dopamine release into the cerebroventricular system of cats. Eur J Pharmacol 135: 1239-242 (1987).

Ryan LJ, Tepper JM, Young SJ and Groves PM. Amphetamine's effects of terminal excitability of noradrenergic locus coeruleus neurons are impulse-dependent at low but not high doses. Brain Res 341: 155-163 (1985a).

Ryan LJ, Tepper JM, Sawyer SF, Young SJ and Groves PM. Autoreceptor activation in central monoamine neurons: Modulation of neurotransmitter release is not mediated by intermittent axonal conduction. neurosci 15: 925-931 (1985b).

Sawyer SF, Tepper JM, Young SJ and Groves PM. Antidromic activation of dorsal raphe neurons from neostriatum: Physiological characterization and effects of terminal autoreceptor stimulation. Brain Res 332: 15-28 (1985).

Stamford JA, Kruk ZL and Millar J. Sub-second striatal dopamine release measured by in vivo voltammetry. Brain Res 381: 351-355 (1985).

Starke K, Reimann W, Zumstein W and Hertting G. Effect of dopamine receptor agonists and antagonists on the release of dopamine in the rabbit caudate nucleud in vitro. Naunyn-Schmeideberg's Arch Pharmacol 305: 27-36 (1978).

Stjarne L. Facilitation and receptor-mediated regulation of noradrenaline secretion by control of recruitment of varicosities as well as by control of electrosecretory coupling. Neuroscience J 1147-1155 (1978).

Takeuchi H, Young SJ and Groves PM. Dopaminergic terminal excitability following arrival of the nerve impulse: The influence of amphetamine and haloperidol. Brain Res 245: 47-56 (1982).

Tepper JM, Nakamura S, Young SJ and Groves PM. Autoreceptor-mediated changes in dopaminergic terminal excitability: Effects of striatal drug infusions. Brain Res 309: 317-333 (1984a).

Tepper JM, Young SJ and Groves PM. Autoreceptor-mediated changes in dopaminergic terminal excitability: Effects of increases in impulse flow. Brain Res 309: 309-316 (1984b).

Tepper JM, Groves PM and Young SJ. The neuropharmacology of the autoinhibition of monoamine release. Trends Pharmacol Sci 6: 251-256 (1985).

Tepper JM, Sawyer SF, Young SJ and Groves PM. Autoreceptor-mediated changes in dopaminergic terminal excitability: Effects of potassium channel blockers. Brain Res 367: 230-237 (1986).

Tepper JM, Gariano RF and Groves PM. The neurophysiology of dopamine nerve terminal autoreceptors. In: Chiodo LA, Freeman AS, eds. Neurophysiology of Dopaminergic Systems: Current Status and Clinical Perspectives. Detroit: Lakeshore, 1987, pp. 93-127.

Verge D, Daval G, Patey A, Gozlon H, Mestikawy S and Hamon M. Presynaptic 5-HT autoreceptors on serotonergic cell bodies and/or dendrites but not terminals are of the $5HT_{1A}$ subtype. Eur J Pharmacol 113: 463-464 (1985).

von Voigtlander PF and Moore KE. Involvement of nigrostriatal neurons in the in vivo release of dopamine by amphetamine, amantadine and tyramine. J Pharmacol Exp Therapeut 184: 542-552 (1973).

Wall PH. Excitability changes in afferent fibre terminations and their relation to slow potentials. J Physiol (Lond) 142: 1-21 (1958).

Williams JT and North RA. Opiate-receptor interactions on single locus coeruleus neurones. Molec Pharmacol 26: 489-497 (1984).

Williams JT and North RA. Catecholamine inhibition of calcium action potentials in rat locus coeruleus neurones. Neurosci 14: 103-109 (1985).

Williams JT, Henderson G and North RA. Characterization of alpha -adrenoceptors which increase potassium conductance in rat locus coeruleus neurones. Neuroscience 14: 95-101 (1985).

Yang CR and Mogenson GJ. Dopamine enhances terminal excitability of hippocampal accumbens neurons via D2 receptor: Role of dopamine in presynaptic inhibition. J Neurosci 6: 2470-2478 (1986).

Zucker RS and Lando L. Mechanism of transmitter release: Voltage hypothesis and calcium hypothesis. Science 231: 574-579 (1986).