Neuroscience Vol. 15, No. 4, pp. 925–931, 1985
Printed in Great Britain

0306-4522/85 $3.00 + 0.00
Pergamon Press Ltd
IBRO

COMMENTARY

AUTORECEPTOR ACTIVATION IN CENTRAL MONOAMINE NEURONS: MODULATION OF NEUROTRANSMITTER RELEASE IS NOT MEDIATED BY INTERMITTENT AXONAL CONDUCTION

L. J. RYAN, J. M. TEPPER, S. F. SAWYER,
S. J. YOUNG and P. M. GROVES*
Department of Psychiatry, University of California, San Diego, La Jolla, CA 92093, U.S.A.

CONTENTS

NEUROTRANSMITTER SECRETION AND AUTORECEPTOR ACTIVATION

Calcium-dependent, stimulus-evoked release of neurotransmitter appears to be modulated by presynaptic receptors located on the axon terminals of monoamine neurons. Some presynaptic receptors are sensitive to a cell's own transmitter and have been termed "autoreceptors". In monoaminergic neurons, autoreceptor stimulation reduces stimulus-evoked neurotransmitter release, whereas autoreceptor blockade enhances neurotransmitter release.[17,31,41] Despite many studies supporting the existence of autoreceptors and describing the effects on evoked transmitter release of autoreceptor stimulation and blockade, the mechanisms by which autoreceptor activation reduces transmitter release are unknown.

One current hypothesis suggests that the modulation of transmitter release by autoreceptors and other presynaptic receptors may be due to recruitment and disrecruitment of neurotransmitter release sites. Recent evidence has indicated that in the peripheral nervous system each action potential may promote neurotransmitter release at only a few of the available release sites.[3,8,9,12–14,23,24,32,40,42,44,45] Similar low probability and intermittent release has also been reported for a central nervous system neuron.[28–30] Intermittent release in the peripheral nervous system has been suggested to result from intermittent conduction of the action potential through the highly varicose sympathetic axon.[12,13,32,42,44,45] Conduction failure would most likely occur at the varicosities along the axon, which are sites of low-safety factor for conduction due to the sudden 3–4-fold enlargement in axonal diameter. In highly varicose axons, conduction failure at a varicosity might act much like a tourniquet, preventing action potential invasion of the entire terminal field distal to the site of conduction failure thereby precluding neurotransmitter release from these sites.

It has been hypothesized that presynaptic receptors reside on the axonal varicosities and that activating these receptors alters the safety factor for impulse propagation,[3,12,13,42,44,45] presumably by changing membrane polarization or conductance. By increasing the probability of conduction failure presynaptic receptor activation could reduce neurotransmitter release. Electrophysiological recordings from the myenteric plexus and the vas deferens have demonstrated that conduction may fail in these sympathetic fibers and that application of noradrenergic or opiate receptor agonists promotes this conduction failure.[12,13,32]

This type of conduction failure resembles in some ways but is distinct from two other kinds of conduction failure that have been proposed to modulate release. One type has been suggested to occur at axonal branch points allowing differential invasion of branches and hence differential release from various portions of the axonal arborization (e.g. Ref. 40). The second type is failure of the action potential to actively propagate into terminal boutons (e.g. Ref. 28).

*To whom all correspondence should be addressed.

ELECTROPHYSIOLOGICAL CONSEQUENCES OF AUTORECEPTOR ACTIVATION IN CENTRAL NERVOUS SYSTEM MONOAMINE NEURONS

In this commentary we consider the possibility that autoreceptor activation reduces neurotransmitter release by causing conduction failure in central monoamine axons. Central monoaminergic neurons resemble peripheral sympathetic neurons in that they have fine, unmyelinated, highly varicose axons. The axons tend to be long and highly branched, with elaborate terminal arborizations. For example, the cortical noradrenergic innervation arising from the locus coeruleus is carried by long tangentially oriented axons that run deep in layer 6. Radially ascending branches arise from these fibers and provide the collateral arborization of layers 1–5. Both the tangentially oriented fibers and the collaterals are thin and highly varicose.[33] The varicosities, which often form *en passant* synapses, are approximately 1.0 μm diameter; the intervaricose axons are about 0.3 μm diameter.[5,37]

Changes in terminal excitability

We have shown previously that stimulation of axonal autoreceptors on central monoaminergic neurons decreases the electrical excitability of dopaminergic, noradrenergic and serotonergic axon terminals in the forebrain of rats.[22,34,35,38,39,47–49] In contrast, autoreceptor blockade increases terminal excitability[22,34,49] as do infusions of the depolarizing agent, potassium.[34,49] In a manner similar to that proposed by Wall,[50] whose conceptions have recently been confirmed by Kocsis and Waxman,[27] we have interpreted the decrease in excitability as indicating that autoreceptor activation is accompanied by a hyperpolarization of the terminal or an alteration in the ionic conductance of the terminal membranes or both, and that autoreceptor blockade has the opposite effect on terminal polarization and conductance. This interpretation is supported by intracellular studies of somatic autoreceptors on monoamine neurons[1,2,16,19] in which autoreceptor activation was shown to hyperpolarize the somatic membrane and, for noradrenergic and serotonergic neurons, to increase its conductance. Thus our evidence suggests that activating autoreceptors should lower the safety factor for conduction and facilitate conduction failure. However, even though the autoreceptor-mediated changes in terminal excitability that we have observed are consistent with the idea that autoreceptor activation could impair impulse conduction in central monoaminergic axons, other aspects of our results suggest that there cannot be failure of action potential propagation in axons of these central neurons.

In our experiments, single-unit discharges were obtained in rats from electrophysiologically identified substantia nigra dopaminergic, locus coeruleus noradrenergic and dorsal raphe serotonergic neurons by conventional means as previously described in detail.[38,39,48,49] Neurons were activated antidromically with monophasic square-wave pulses of 0.1–3.0 mA and 0.03–0.5 ms duration, delivered through bipolar stainless-steel enamel-coated electrodes with tip separations of approximately 250 μm, usually at a rate of 1/s. Stimulating electrodes were placed within the ipsilateral neostriatum for dopaminergic neurons, within both the ipsilateral and contralateral neostriatum for serotonergic neurons, and in ipsilateral frontal cortex for noradrenergic neurons.

Autoreceptor activation does not impair antidromic action potential propagation

Antidromic responses elicited from a noradrenergic locus coeruleus neuron (A), a serotonergic dorsal raphe neuron (B) and a dopaminergic substantia nigra neuron (C) are shown in Fig. 1. Prior to drug administration, it was possible to adjust the stimulating current such that it was just sufficient to elicit an antidromic response to every stimulus (Figs 1A–C, top traces). This minimum current was defined as the threshold. In every monoaminergic neuron tested ($n > 600$) it was possible to establish such a threshold, indicating that axonal conduction did not fail intermittently under these test conditions.

Autoreceptor activation reliably increased the threshold current for all three types of monoaminergic neurons.[38,39,48,49] In the experiments shown in Fig. 1, terminal autoreceptors were activated by i.v. injection of the indirect-acting agonist amphetamine (0.5 mg/kg for dopamine neurons; 5.0 mg/kg for noradrenergic neurons) or the direct-acting serotonin agonist 5-methoxy-*N*,*N*-dimethyltroptamine (0.04 mg/kg for serotonin neurons). After agonist administration, the pre-drug threshold currents became insufficient to elicit 100% antidromic responding (Figs 1A–C, middle traces). Although the threshold increased, in every case ($n = 43$; for these drugs at these doses) 100% antidromic responding could be reinstated by increasing the stimulus current (Figs 1A–C, bottom traces). Thus, despite the marked decrease in excitability subsequent to terminal autoreceptor stimulation, there were no instances of impulse failure at any point between the site of stimulation and site of recording in any of the three kinds of monoaminergic neurons. In several hundred cases of autoreceptor stimulation of central monoaminergic neurons, either by systemic administration or local infusion of agonists into the terminal fields, there were no instances in which 100% antidromic responding could not be reinstated by relatively small increases (5–50%) in stimulus current.

In contrast, when the depolarizing agent, potassium chloride, was infused directly into the neostriatal terminal fields of dopaminergic substantia nigra neurons, the threshold usually dropped, indicating depolarization of the terminals. In one case, however, the threshold initially fell but then rose rapidly until antidromic responses could no longer be elicited even by very high currents (> 5 mA). After

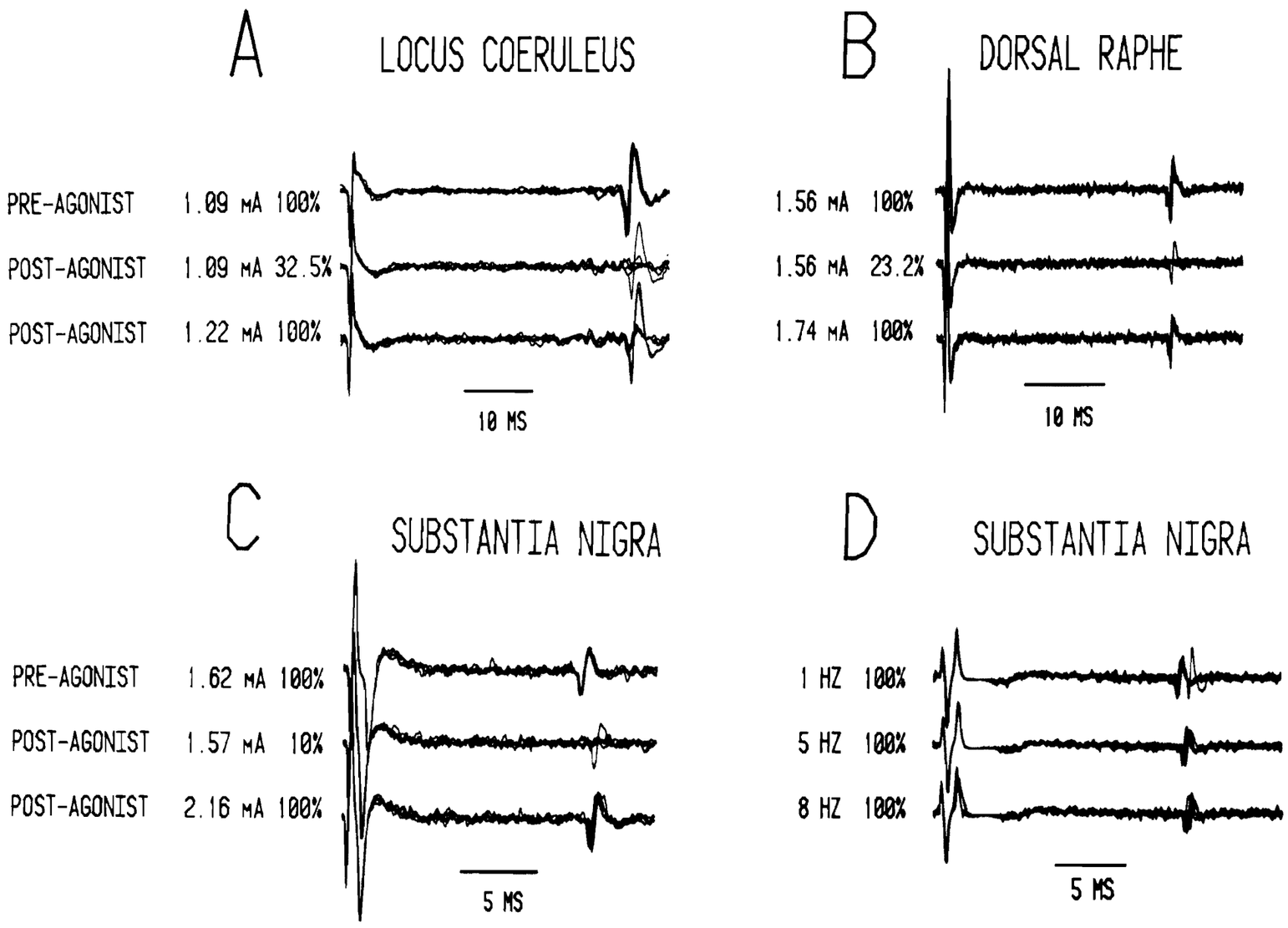

Fig. 1. The i.v. administration of agonist drugs raises the threshold for eliciting antidromic responses from the terminal fields of noradrenergic locus coeruleus (A), serotonergic dorsal raphe (B) and dopaminergic substantia nigra (C) neurons. Prior to drug administration, the threshold current (minimum current at which an antidromic response could be provoked by every stimulus) was determined. In the upper traces in (A)–(C) five responses evoked by the threshold current are overlaid. Antidromic responses to 100% of the stimuli were observed. Within 60 s of the i.v. administration of the agonist drugs [(A) 5.0 mg/kg amphetamine after an earlier injection of 0.25 mg/kg amphetamine; (B) 0.04 mg/kg 5-methoxy-*N*,*N*-dimethyltrytamine; (C) 0.5 mg/kg amphetamine] this current elicits an antidromic response to only 32, 23 and 10%, respectively, of the stimuli as shown in the middle trace [in (C) a slightly smaller current, which produced 50.1% responding prior to the drug, is shown since the original threshold current was not retested in this case]. A higher current, capable of reinstating 100% responding, could always be found, as shown in the bottom traces. In (A) and (C) only the initial segment antidromic response in seen following some of the stimuli. In (D) 100% antidromic responding is shown to suprathreshold stimulation across the physiologically relevant range of firing rates for a substantia nigra neuron. A single full antidromic spike is seen following the antidromic A-spike in the 1-Hz trace. The latency and latency variability increase as the higher frequency stimulations progress.

several minutes the threshold dropped and 100% antidromic responding was reinstated. In this example conduction failure appears to have occurred because of depolarization block.[49]

Our results then suggest that impulse-conduction failure, as described in peripheral sympathetic axons,[12,13,32] does not occur in central monoaminergic neurons. Although noradrenergic, dopaminergic and serotonergic neurons respond to terminal autoreceptor stimulation with a decrease in antidromic excitability, the observation that, in every case, 100% antidromic responding could be reinstated by relatively small increments in current strength argues against conduction failure at any point along the axon between the site of stimulation and site of recording. Thus it is unlikely that terminal autoreceptor stimulation leads to a reduction in transmitter release in central monoaminergic neurons by causing presynaptic impulses to fail proximal to sites of release.

POSSIBLE AMBIGUITIES IN THE INTERPRETATION OF ANTIDROMIC ACTIVATION EXPERIMENTS

It could be argued that impulse-conduction failure does occur in these axons, but that we failed to observe it due to our methods of stimulation and excitability testing. Several such sources of error are considered.

Site of antidromic action potential initiation

Insofar as we are stimulating within the central nervous system it is difficult to specify precisely the site along the axon at which action potential initiation occurs. There are several reasons, though, for believing that in our experiments action potential initiation within the terminal fields is occurring near the location of presynaptic autoreceptors. (1) Changes in excitability following drug administration are seen when the stimulating electrode is positioned

within the terminal field and the drug reaches the terminal field as happens when it is administered systemically or by direct infusion into the terminal field. No changes in terminal excitability are seen following drug infusion into non-terminal portions of the axonal trajectory. (2) Changes in excitability are not seen when the stimulating electrode is positioned along the axon's preterminal path in the medial forebrain bundle for the substantia nigra[22] and dorsal raphe[39] and in the dorsal noradrenergic pathway for the locus coeruleus,[34] regardless of where the drug is administered. (3) The antidromic responses of individual neurons were often observed to occur at multiple discrete latencies, as has previously been described.[11,22,48] These multiple latencies were seen both before and after drug administration.[39,49] Hence, impulse initiation can occur at many different sites within the terminal arborization. As these latencies may differ by several milliseconds, the sites of initiation must be separated by several millimetres of axonal length and, as others have suggested, are probably on separate axon branches.[11,49]

Absence of conduction failure: inappropriate stimulating frequencies?

One might argue that inappropriate stimulating frequencies were used in our experiments. In sympathetic neurons, conduction failure was most prominent at low frequencies of stimulation (< 3 Hz) but did not occur at higher frequencies (> 8 Hz).[12] In contrast, in other non-varicose neurons, conduction failure has been reported to occur primarily at high frequencies.[40,46] However, for virtually all cells tested at frequencies of stimulation between 0.3 and 10 Hz, we were able to promote 100% antidromic responding. This is illustrated for a dopaminergic neuron in Fig. 1(D). The neostriatal terminal field was stimulated with suprathreshold (1.5 × threshold) current at frequencies of 1, 5 and 8 Hz, the approximate range over which these neurons are spontaneously active *in vivo*.[49] Although the antidromic latency and variability of the response increased at the higher stimulation frequencies, there were no instances of conduction failure. The only exceptions were some raphe neurons which failed to faithfully follow 10-Hz stimulation after 2–3 s of stimulation.[39] However, as this failure occurred following stimulation of the medial forebrain bundle, as well as after stimulation of the neostriatal terminal fields, the conduction failure probably reflects the build-up of an axonal subnormal period[6,46] rather than autoreceptor activation.

Latency changes following autoreceptor activation: does the site of initiation shift to bypass a conduction block?

Another possible objection is that because the threshold currents increased after autoreceptor agonist administration, the site of action potential initiation might have shifted towards the soma, bypassing the presumed conduction block. However, in most cases, especially for dopaminergic and noradrenergic neurons, but less reliably for serotonergic neurons, the administration of an autoreceptor agonist produced an increase in the latency of the antidromic response, even at the higher post-drug current settings, rather than the decreased latency one should observe if the site of initiation had shifted closer to the soma. This occurs after both local infusion and systemic administration of agonist drugs. Conversely, antagonists lead to a decrease in response latency even at the lower threshold current.[34,49] An example is shown for a dopaminergic neuron in Fig. 2. In this example, 0.01 mM amphetamine was infused by pressure injection into the neostriatum adjacent to the stimulating electrode (as per Ref. 49). Prior to agonist infusion, the latency of the antidromic response was relatively stable. Stimulation for all traces in this figure was at the original threshold current. Beginning 120 s after the start of the infusion, the threshold rose as indicated by the stimulating current no longer producing 100% antidromic responding and the response latency became longer and more variable. The increase in latency was continuous, rather than saltant, as shown by the progressively longer latencies seen as the infusion proceeded. Thus, the increased latency following autoreceptor stimulation suggests a reduction in conduction velocity and this, coupled with the threshold increase, indicates that the action potential must traverse axonal membrane that is

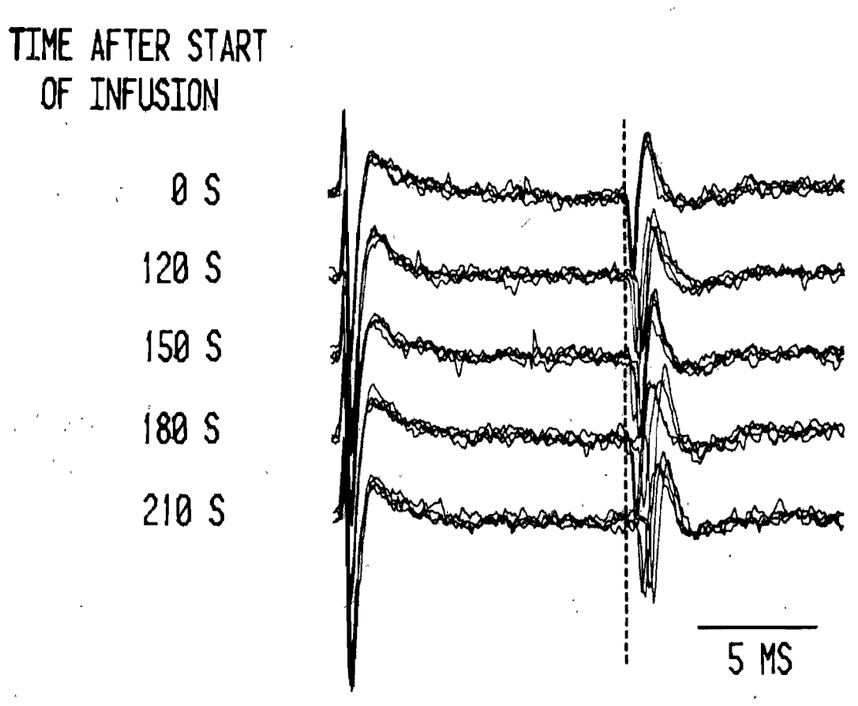

Fig. 2. The latency and the latency variability of the antidromic response of a dopaminergic substantia nigra neuron to stimulation of the head of the neostriatum increases during the infusion of the indirect dopamine agonist, 0.1 mM amphetamine, into the neostriatum near the stimulating electrode. The latency shift began approximately 120 s after the start of the infusion, at the time when the threshold rose and the stimulating current became insufficient to evoke an antidromic action potential to every stimulus. In the figure, five consecutive antidromic responses (skipping collisions and stimuli that failed to elicit a response) beginning at the times indicated are superimposed. Stimulation was at the pre-infusion threshold current (100% antidromic responding; 1.20 mA, 0.2 ms) for all traces.

hyperpolarized or the conductance of which is increased.[46] Similar changes in latency were never observed following infusion of agonists into non-terminal portions of the axonal trajectory, such as into the medial forebrain bundle.[49]

It is also possible that the site of action potential initiation shifted from one terminal branch to a higher threshold branch invested with fewer autoreceptors. This seems unlikely, however, since the latency always increased, the latency change was gradual and when multiple latencies were present prior to drug administration, the same relative multiple latencies were usually seen after administration.

However, we should note that conduction failure might occur in the finest terminal twigs as our method cannot exclude the possibility of conduction failure distal to the site of antidromic action potential initiation.

Conduction failure: orthodromic vs antidromic propagation.

It might also be suggested that impulse-conduction failure is more likely for orthodromic conduction than for antidromic conduction. This is unlikely, however, because we never observed orthodromic conduction failure; we always observed collisions with the antidromic action potential whenever a spontaneous orthodromic spike occurred within the appropriate collision interval. Furthermore, electron microscopic analyses of identified monoaminergic axonal varicosities and intervaricose segments from this laboratory and others[4,5,20,21] have not revealed any morphological polarizations that could account for such a directional sensitivity. Indeed, conduction failure is more likely to occur when the action potential travels antidromically, since the action potential must invade larger diameter main axons from smaller diameter branches.[46]

MECHANISMS OF AUTORECEPTOR MEDIATED CHANGES IN NEUROTRANSMITTER RELEASE

The reliability of axonal conduction in neurons of these three central monoaminergic nuclei suggests that autoreceptors do not regulate transmitter release by preventing action potential propagation along the varicose portion of the axon, thereby precluding transmitter release in the entire terminal field distal to the site of conduction failure. Terminal autoreceptor activation in central monoamine neurons probably modulates neurotransmitter release by altering other aspects of the release process once the action potential has reached the varicosities. This may represent a true difference in the factors controlling neurotransmitter secretion in the central and peripheral nervous systems and could perhaps have functional significance related to the kinds of neurotransmission these different neurons subserve: postganglionic sympathetic synapses lack specialized synaptic contacts, releasing transmitter into a wide synaptic cleft,[7] in contrast to central monoamine neurons, which have been shown to form classical, morphologically specialized synapses at most, if not all, sites where they have been carefully examined.[10,20,21,37]

Biochemical studies also suggest that autoreceptors act not by blocking action potential conduction, but rather by altering the magnitude of the action potential-induced terminal depolarization or by altering ionic currents within the terminal. For instance, in rat whole brain synaptosomal suspensions, alpha$_2$ autoreceptor agonists reduced norepinephrine release provoked by K^+-induced depolarization;[15] reduced Ca^{2+} increased the sensitivity of the synaptosomes to autoreceptor-mediated inhibition of release. In rabbit caudate slices, autoreceptor control of K^+-evoked dopamine release is resistant to action potential suppression by the addition of tetrodotoxin to the bathing medium.[25] In a like manner, tetrodotoxin also failed to alter autoreceptor regulation of serotonin release induced by high Ca^{2+} levels from rat neocortical slices.[17] Autoreceptors, however, only regulate calcium-dependent neurotransmitter release and do not alter release induced by drugs such as tyramine (e.g. Ref. 26). These and many similar observations suggest that autoreceptor activation regulates neurotransmitter release by altering electrical or ionic events within the synaptic terminal.

Our results are not necessarily inconsistent with the proposition that secretion from central monoamine varicosities is all-or-none and intermittent. This might occur through mechanisms other than conduction failure and the subsequent cutting off of release from entire terminal branches. All-or-none and intermittent synaptic release has been suggested recently for several different non-monoamine synapses and non-varicose axons and has been attributed to factors other than conduction failure.[28–30,36,40] We might speculate that, in central monoamine neurons, autoreceptor activation causes local impulse failure only within the varicosities, perhaps as a consequence of a hyperpolarization or a reduction in transmembrane resistance, or both. Alternatively, it may be that under normal conditions the membrane of the varicosities does not actively propagate the action potential[3,43,45] and activating autoreceptors could reduce the action potential-induced passive depolarization of the varicosities, thereby reducing the voltage-dependent calcium current sufficiently to prevent transmitter release. The reduction in axonal diameter at intervaricose segment might favor the reinitiation of the action potential on the distal side of the varicosity, allowing the impulse to propagate further along the axon. Hence the intermittency of release and the modulation of release by autoreceptors need not depend upon intermittency of neuronal conduction.

Intermittent release due to variation in factors other than conduction failure has been clearly demonstrated in a synapse made onto the Mauthner cell.[28–30] As the afferent fibers enter the glial cap

surrounding the Mauthner cell body, impulse conduction always fails. Beyond this point the afferents branch and the terminal boutons formed show intermittent release. In this case, intermittent release cannot be attributed to failure of action potential conduction, since propagation always fails. Rather, intermittent release must be attributed to variability in stimulus–secretion coupling, much as we suggest occurs for central monoamine terminals. Whether autoreceptors are involved in this process is unknown at present.

Regardless of whether neurotransmitter release from central monoamine varicosities is all-or-none or is graded, the results reviewed in this commentary suggest that autoreceptor activation modulates neurotransmitter release by altering the magnitude of action potential-induced depolarization or the coupling of depolarization with secretion, or both, and not by causing action potential failure that prevents neurotransmitter release from entire fields of the terminal arborization.

Acknowledgements—This research was supported in part by Grants DA 02854 and RSA DA 00079 (to P. M. Groves) from the National Institute on Drug Abuse.

REFERENCES

1. Aghajanian G. K. and Lakoski J. M. (1984) Hyperpolarization of serotonergic neurons by serotonin and LSD: studies in brain slices showing increased K^+ conductance. *Brain Res.* **305,** 353–361.
2. Aghajanian G. K. and VanderMaelen C. P. (1982) Alpha$_2$-adrenoceptor-mediated hyperpolarization of locus coeruleus neurons: intracellular studies *in vivo*. *Science, Wash.* **215,** 1394–1396.
3. Alberts P., Bartfai T. and Stjärne L. (1981) Site(s) and mechanisms of autoinhibition and facilitation of [^{3}H]noradrenaline secretion in guinea pig vas deferens. *J. Physiol., Lond.* **312,** 297–334.
4. Arluison M. and de La Manche I. S. (1980) High-resolution radioautographic study of the serotonin innervation of the rat corpus striatum after intraventricular administration of [^{3}H]5-hydroxyltryptamine. *Neuroscience* **5,** 229–240.
5. Arluison M., Agid Y. and Javoy F. (1978) Dopaminergic nerve endings in the neostriatum of the rat. 1. Identification by intracerebral injections of 5-hydroxydopamine. *Neuroscience* **3,** 657–673.
6. Aston-Jones G., Segal M. and Bloom F. E. (1980) Brain aminergic axons exhibit marked variability in conduction velocity. *Brain Res.* **195,** 215–222.
7. Bennett M. R. (1972) *Autonomic Neuromuscular Transmission.* Cambridge University Press, Cambridge, England.
8. Blakeley A. G. H. and Cunnane T. C. (1979) The packeted release of transmitter from the sympathetic nerves of guinea-pig vas deferens: an electrophysiological study. *J. Physiol., Lond.* **296,** 85–96.
9. Blakeley A. G. H., Cunnane T. C. and Petersen S. A. (1982) Local regulation of transmitter release from rodent sympathetic nerve terminals? *J. Physiol., Lond.* **325,** 93–109.
10. Chan-Palay V. (1978) The paratrigeminal nucleus. II. Identification and inter-relations of catecholamine axons, indolamine axons, and substance P-immunoreactive cells in the neuropil. *J. Neurocytol.* **7,** 419–442.
11. Collingridge G. L., James T. A. and MacLeod N. K. Antidromic latency variations of nigral compacta neurons. *Experientia* **36,** 970–971.
12. Cunnane T. C. and Stjärne L. (1982) Secretion of transmitter from individual varicosities of guinea-pig and mouse vas deferens: all-or-none and extremely intermittent. *Neuroscience* **7,** 2565–2576.
13. Cunnane T. C. and Stjärne L. (1984) Frequency dependent intermittency and ionic basis of impulse conduction in postganglionic sympathetic fibres of guinea-pig vas deferens. *Neuroscience* **11,** 211–229.
14. Cunnane T. C. and Stjärne L. (1984) Transmitter secretion from individual varicosities of guinea-pig and mouse vas deferens: highly intermittent and monoquantal. *Neuroscience* **13,** 1–20.
15. De Langen C. D. J., Hogenboom F. and Mulder A. H. (1979) Presynaptic noradrenergic alpha-receptors and modulation of ^{3}H-noradrenaline release from rat brain synaptosomes. *Eur. J. Pharmac.* **60,** 79–89.
16. Egan T. M., Henderson G., North R. A. and Williams J. T. (1983) Noradrenaline-mediated synaptic inhibition in rat locus coeruleus neurones. *J. Physiol., Lond.* **345,** 477–488.
17. Gothert M. (1980) Serotonin-receptor-mediated modulation of Ca^{2+}-dependent 5-hydroxytryptamine release from neurones of the rat brain cortex. *Naunyn-Schmiedebergs Arch. Pharmac.* **314,** 223–230.
18. Gothert M. (1982) Modulation of serotonin release in the brain via presynaptic receptors. *Trends Pharmac. Sci.* **3,** 437–440.
19. Grace A. A. and Bunney B. S. (1983) Intracellular and extracellular electrophysiology of nigral dopaminergic neurons—1. Identification and characterization. *Neuroscience* **10,** 301–315.
20. Groves P. (1980) Synaptic endings and their postsynaptic targets in neostriatum: synaptic specializations revealed from analysis of serial sections. *Proc. natn. Acad. Sci. U.S.A.* **77,** 6926–6929.
21. Groves P. M. and Wilson C. J. (1980) Monoaminergic presynaptic axons and dendrites in rat locus coeruleus seen in reconstructions of serial sections. *J. comp. Neurol.* **193,** 853–862.
22. Groves P. M., Fenster G. A., Tepper J. M., Nakamura S. and Young S. J. (1981) Changes in dopaminergic terminal excitability induced by amphetamine and haloperidol. *Brain Res.* **221,** 425–431.
23. Hirst G. D. S. and Neild T. O. (1980) Some properties of spontaneous excitatory junction potentials recorded from arterioles of guinea-pigs. *J. Physiol., Lond.* **303,** 43–60.
24. Holman M. E. and Suprenant A. (1980) Effects of tetraethylammonium chloride on sympathetic neuromuscular transmission in saphenous artery of young rabbits. *J. Physiol., Lond.* **305,** 451–465.
25. Jackisch R., Zumstein A., Hertting G. and Starke K. (1980) Interneurons are probably not involved in the presynaptic dopaminergic control of dopamine release in rabbit caudate nucleus. *Naunyn-Schmiedebergs Arch. Pharmac.* **314,** 129–133.
26. Kamal L. A., Arbilla S. and Langer S. Z. (1981) Presynaptic modulation of the release of dopamine from the rabbit caudate nucleus: differences between electrical stimulation, amphetamine and tyramine. *J. Pharmac. exp. Ther.* **216,** 592–598.

27. Kocsis J. D. and Waxman S. G. (1982) Intra-axonal recordings in rat dorsal column axons: membrane hyperpolarization and decreased excitability precede the primary afferent depolarization. *Brain Res.* **238,** 222–227.
28. Korn H., Faber D. S., Burnod Y. and Triller A. (1984) Regulation of efficacy at central synapses. *J. Neurosci.* **4,** 125–130.
29. Korn H., Mallet A., Triller A. and Faber D. S. (1982) Transmission at a central inhibitory synapse. II. Quantal description of release, with a physical correlate for binomial *n. J. Neurophysical.* **48,** 679–707.
30. Korn H., Triller A., Mallet A. and Faber D. S. (1981) Fluctuating responses at a central synapse: *n* of binomial fit predicts number of stained presynaptic boutons. *Science, Wash.* **213,** 898–901.
31. Langer S. Z. (1977) Presynaptic receptors and their role in the regulation of transmitter release. *Br. J. Pharmac.* **60,** 481–497.
32. Morita K. and North R. A. (1981) Opiates and enkephalin reduce the excitability of neuronal processes. *Neuroscience* **10,** 1943–1951.
33. Morrison J. H., Foote S. L., O'Connor D. O. and Bloom F. E. (1982) Laminar, tangential and regional organization of the noradrenergic innervation of monkey cortex: dopamine-beta-hydroxylase immunohistochemistry. *Brain Res. Bull.* **9,** 309–319.
34. Nakamura S., Tepper J. M., Young S. J. and Groves P. M. (1981) Neurophysiological consequences of presynaptic receptor activation: changes in noradrenergic terminal excitability. *Brain Res.* **226,** 155–170.
35. Nakamura S., Tepper J. M., Young S. J. and Groves P. M. (1982) Changes in noradrenergic terminal excitability induced by amphetamine and their relation to impulse traffic. *Neuroscience* **7,** 2217–2224.
36. Neale E. A., Nelson P. G., Macdonald R. L., Christian C. N. and Bowers L. M. (1983) Synaptic interactions between mammalian central neurons in cell culture. III. Morphological correlates of quantal synaptic transmission. *J. Neurophysiol.* **49,** 1459–1468.
37. Olschowska J. A., Molliver M. E., Grzanna R., Rice F. L. and Coyle J. T. (1981) Ultrastructural demonstration of noradrenergic synapses in the rat central nervous system by dopamine-beta-hydroxylase immunocytochemistry. *J. Histochem. Cytochem.* **29,** 271–280.
38. Ryan L. J., Tepper J. M., Young S. J. and Groves P. M. (1985) Amphetamine's effects on terminal excitability of noradrenergic locus coeruleus neurons are impulse-dependent at low but not high doses. *Brain Res.* In Press.
39. Sawyer S. F., Tepper J. M., Young S. J. and Groves P. M. (1985) Antidromic activation of dorsal raphe neurons from neostriatum: physiological characterization and effects of terminal autoreceptor activation. *Brain Res.* In press.
40. Smith D. O. (1983) Variable activation of synaptic release sites at the neuromuscular junction. *Expl Neurol.* **80,** 520–528.
41. Starke K. (1981) Presynaptic receptors. *A. Rev. Pharmac. Toxicol.* **21,** 7–30.
42. Stjärne L. (1978) Facilitation and receptor-mediated regulation of noradrenaline secretion by control of recruitment of varicosities as well as by control of electro-secretory coupling. *Neuroscience* **3,** 1147–1155.
43. Stjärne L. (1979) Current issues in the study of norepinephrine secretion from noradrenergic nerves. In *Catecholamines: Basic and Clinical Frontiers* (eds Usdin E., Kopin I. J. and Barchas J.), pp. 240–243. Pergamon Press, Oxford.
44. Stjärne L. (1981) On sites and mechanisms of presynaptic control of noradrenaline secretion. In *Chemical Neurotransmission 75 Years* (eds Stjärne L., Hedqvist P., Lagercrantz H. and Wennmalm A.), pp. 153–164. Academic Press, London.
45. Stjärne L. (1982) Site(s) and ionic mechanisms in facilitation and alpha-excitation of ^{3}H-noradreneraline secretion in guinea-pig vas deferens. In *Neurotransmitter Receptors, Advances in Pharmacology and Therapeutics* II, Vol. 2 (eds Yoshida H., Hagihara Y. and Ebashi S.), pp. 111–120. Pergamon Press, Oxford.
46. Swadlow H. A., Kocsis J. D. and Waxman S. G. (1980) Modulation of impulse conduction along the axonal tree. *A. Rev. biophys. Bioengng* **9,** 143–179.
47. Takeuchi H., Young S. J. and Groves P. M. (1982) Dopaminergic terminal excitability following arrival of the nerve impulse: the influence of amphetamine and haloperidol. *Brain Res.* **245,** 47–56.
48. Tepper J. M., Young S. J. and Groves P. M. (1984) Autoreceptor-mediated changes in dopaminergic terminal excitability: effects of increases in impulse flow. *Brain Res.* **309,** 309–316.
49. Tepper J. M., Nakamura S., Young S. J. and Groves P. M. (1984) Autoreceptor-mediated changes in dopaminergic terminal excitability: effects of striatal drug infusions. *Brain Res.* **309,** 317–333.
50. Wall P. D. (1958) Excitability changes in afferent fibre terminations and their relation to slow potentials. *J. Physiol., Lond.* **142,** 1–21.

(*Accepted* 12 *February* 1985)