PHARM REV

PHARMACOLOGICAL REVIEWS

Role of High-Affinity Receptors and Membrane Transporters in Nonsynaptic Communication and Drug Action in the Central Nervous System

E. SYLVESTER VIZI

Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary

This paper is available online at http://www.pharmrev.org

Abstract——Neurochemical and morphological evidence has shown that some neurotransmitters or substances may be released from both synaptic and nonsynaptic sites for diffusion to target cells more distant than those observed in regular synaptic transmission. There are functional interactions between neurons without synaptic contacts, and matches between release sites and localization of receptors sensitive to the chemical signal are exceptions rather than the rule in the central nervous system. This also indicates that besides cabled information signaling (through synapses), there is a "wireless" nonsynaptic interaction between axon terminals. This would be a form of communication transitional between discrete classical neurotransmission (in Sherrington's synapse) and the relatively nonspecific neuroendocrine secretion. Recent findings indicate that in addition to monoamines (norepinephrine, dopamine, serotonin), other transmitters, such as acetylcholine and nitric oxide (NO), may also be involved in these nonsynaptic interactions. It has been shown that NO, an ideal mediator of nonsynaptic communication, can influence the function of uptake carrier systems, which may be an important factor in the regulation of extracellular concentration of different transmitters. This review will focus on the role of nonsynaptic receptors and transporters in presynaptic modulation of chemical transmission in the central nervous system. The nonsynaptic interaction between neurons mediated via receptors and transports of high affinity not localized in synapses has the potential to be an important contributor to the properties and function of neuronal networks. In addition, it will be suggested for the first time that the receptors and transporters expressed nonsynaptically and being of high affinity are the target of drugs taken by the patient.

I. Introduction

Our understanding of chemical signal transmission between neurons and between axon terminals and target cells has advanced significantly since Elliott (1904), Loewi (1921), and Dale (1934) first elaborated on the concept that epinephrine and acetylcholine (ACh)[2] are released from the neuron and may be able to transmit signals toward target cells. Today, our knowledge of how information is conveyed chemically from one cell to another has been heavily influenced by textbook data on the neuromuscular junction (Katz, 1969), in which the transmitter ACh is stored in vesicles and released into the junctional gap in quanta. This system is adopted for very fast signaling: The information transfer occurs within millisecond time intervals and is able to transmit messages of several hundred impulses per second. Each synaptic vesicle releases a quantum of 7000 to 12,000 ACh molecules into the narrow junctional cleft, raising the local concentration to the millimolar range (Kuffler and Yoshikami, 1975; cf. Van der Kloot and Molgo, 1994). Under this condition, the receptors receiving the chemical messages are of low affinity. As far as the structure for chemical information processing is concerned, since the work of Ramon-y-Cajal (1893) and Sherrington (1906), much of our current knowledge comes from studies based on junctional architecture (cf. Tansey, 1998). The idea that the transmitter is released in quanta on the arrival of the action potential is well established and has been accepted at the neuromuscular junction, but it is not at all clear that this is the case at the autonomic neuroeffector transmission site. In contrast to striatal muscle, autonomic neuroeffector systems are thus not organized in units, but the innervation is quite diffuse. The quantal release is less clearly established in the central nervous system (CNS), although evidence is presented that this is probably the case. Accordingly, the brain was considered a telephone network that receives signals via synapse processing by means of a high concentration of transmitters through receptors. A chemical signal transmission system that primarily uses synaptic transmission in the CNS possesses several characteristics. Because transmitter concentration in the synaptic gap can be high ($\sim$0.01–1 mM), the receptors expressed on both presynaptic and postsynaptic sites are of low affinity (MacDermott et al., 1999). Additionally, once released, the transmitter is removed from the cleft either enzymatically or by an uptake system and by diffusion.

One well characterized mechanism by which chemical neurotransmission can be modulated is the presynaptic modulation of transmitter release via presynaptic receptors expressed on axon terminals. Activation of these receptors by endogenous or exogenous ligands results in inhibition or facilitation of the amount of transmitters released into the extracellular space by an action potential (Starke et al., 1977, 1989; Westfall 1977; cf. Starke, 1981; Langer, 1981a; Vizi, 1979; Muscholl, 1980a,b; Kal-

[1] Address for correspondence: Dr. E. Sylvester Vizi, Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, POB 67, H-1450 Budapest, Hungary. E-mail: ESVIZI@KOKI.HU

[2] Abbreviations: ACh, acetylcholine; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; $[Ca^{2+}]_o$, extracellular Ca^{2+} concentration; $[Na^+]_i$, intracellular Na^+ concentration; CNS, central nervous system; DA, dopamine; DAT, dopamine transporter; GABA, γ-aminobutyric acid; Glu, glutamate; IPSP, inhibitory postsynaptic potential; KA, kainate; nAChR, nicotinic acetylcholine receptor; NE, norepinephrine; NET, norepinephrine transporter; NMDA, *N*-methyl-D-aspartic acid; NO, nitric oxide; PKC, protein kinase C; 5-HT, serotonin; TTX, tetrodotoxin.

sner and Westfall, 1990; Wu and Saggau, 1997). It is interesting to note that Koelle (1990) mentioned in his review that the first concrete evidence of presynaptic receptors was published in a classic report by Masland and Wigton (1940). These authors claimed that the fasciculation that follows the intra-arterial injection of ACh or an anticholinesterase drug into a skeletal muscle reflects the firing of the motor units rather than stimulation of the muscle fibers. The other possibility to modulate the extracellular concentration of transmitters, once released, is their removal by one of the Na^+/Cl^--dependent neurotransmitter transporters. The transporter is a plasma membrane protein that operates by reuptake of the released transmitter. The tricyclic antidepressants exert their effect on monoamine transporters by prolonging the time needed for clearance of transmitters from the extracellular space.

Neurochemical (Vizi, 1980, 1984; cf. Vizi and Kiss, 1998) and morphological (Descarries et al., 1987; Oleskevich et al., 1989; Umbriaco et al., 1995) evidence has shown that some neurotransmitters may be released from both synaptic and nonsynaptic sites (Fig. 1) for diffusion to target cells more distant than those observed in synaptic transmission. It has been shown in the gut and brain that in response to activation of the noradrenergic neurons, there was an α-adrenoceptor-mediated inhibition of ACh release from neighboring cholinergic terminals (Vizi and Knoll, 1971, 1976; Vizi, 1974, 1980b) without any morphologic (synaptic) contact between them. These findings indicate that there is functional interaction (presynaptic inhibition) between neurons without any morphological contact (cf. Vizi, 1980a, 1984a). This was supported by the fact that matches between release sites and localization of receptors sensitive to the chemical signal are exceptions rather than the rule (Herkenham, 1987). Although the disparities between axon terminals (release sites) and receptors were noted in several reports (cf. Herkenham, 1991), Herkenham was the first who studied this mismatch carefully. Even in the report on substance P receptors (Rothman et al., 1984), they put forth that mismatches were the rule rather than the exception. The conclusion (Herkenham, 1987; McLean et al., 1987) drawn from this "mismatch" problem was that mismatches reflect on the existence of high-affinity nonsynaptic receptors that are able to mediate "parasynaptic" (Schmitt, 1984) signal transmission. The nonsynaptic interactions between neurons would be a form of communication transitional between discrete classic neurotransmission (in Sherrington's synapse) and the relatively nonspecific neuroendocrine secretion. Recent findings indicate that in addition to monoamines [norepinephrine (NE), dopamine (DA), and serotonin(5-hydroxytryptamine, or 5-HT)], other transmitters, such as ACh (Descarries et al., 1997) and nitric oxide (NO; Dawson and Snyder, 1994), also may be involved in these nonsynaptic interactions. NO can influence the function
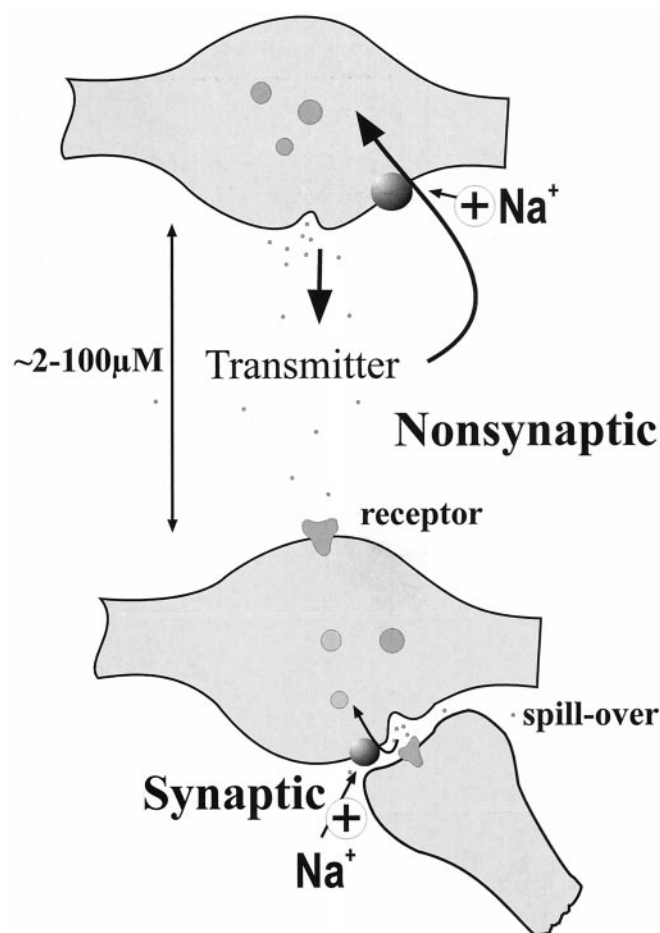
FIG. 1. Synaptic and nonsynaptic interaction between neurons. The transmitter release from varicosity without synaptic contact diffuses far away from the release site and activates remote receptors of high affinity. The transmitter concentration in the extracellular space is low and drops in a function of 3. In the synapse, the transmitter concentration is very high, and there is a possibility of spillover. Transmitter released is taken up by plasma membrane transporters located in the synapse or extrasynaptically.

of uptake carrier systems (Cutillas et al., 1998; Kiss et al., 1999), which may be an important factor in the regulation of extracellular concentration of different transmitters (Gainetdinov et al., 1998; Segovia and Mora, 1998).

This review focuses on the role of nonsynaptic receptors and transporters in presynaptic modulation of chemical transmission in the CNS, and I outline some of the potential points at which we might expect the occurrence of nonsynaptic functional interaction between neurons. It should be clear from this review that nonsynaptic interaction between neurons mediated via receptors and transporters of high affinity not localized in synapses has the potential to be an important contributor to the properties and function of neuronal networks. In addition, receptors and transporters expressed nonsynaptically and of high affinity are the target of drugs taken by the patient.

II. Modulation of Neurochemical Transmission: Role of Receptors and Plasma Membrane Transporters

A. Presynaptic Receptor-Mediated Modulation of Transmitter Release

Action potential at the nerve terminal results in an increase in Ca^{2+} influx through Ca^{2+} channels, activating Ca^{2+} sensors, which in turn trigger the release machinery to cause vesicle fusion and transmitter release (cf. Llinas, 1977). Extracellular Ca^{2+} concentration ($[Ca^{2+}]_o$)-dependent release of transmitters [glutamate (Glu): Uchihashi et al., 1998; Nakai et al., 1999; DA: Milusheva et al., 1992, 1996; and NE: West and Fillenz, 1980) is vesicular (Katz, 1969)], has a high requirement for energy, and is very sensitive to the intracellular ATP level. The $[Ca^{2+}]_o$-dependent release can be blocked by tetrodotoxin and subjected to presynaptic modulation via activation of different presynaptic receptors (Table 1).

It was not until the late 1960s that the concept of presynaptic receptors (i.e., receptors on nerve endings, as opposed to postsynaptic receptors on effector cells) was proposed and the hypothesis was advanced that presynaptic receptor mechanisms are involved in the modulation of neuronal ACh and NE release via α- and muscarinic heteroreceptors (Lindmar et al., 1968; Vizi, 1968; Löffelholz and Muscholl, 1969a,b; Paton and Vizi, 1969).

In 1971, in different laboratories (De Potter and Chubb, 1971; Farnebo and Hamberger, 1971; Kirpekar and Puig, 1971; Starke, 1971), NE was shown to inhibit its own release from noradrenergic terminals via presynaptic α-adrenoceptors. This was named "negative feedback" modulation. Later, similar autoreceptor-mediated modulation was described for other transmitters. It was even shown that there is a positive feedback modulation when the transmitter released into the synaptic cleft increases its own release via stimulation of receptors located on terminals from which the transmitter is released.

The release of transmitter is subjected to presynaptic receptor-mediated modulation (Langer, 1977, 1981a; Nicoll and Alger, 1979; Vizi, 1979, 1984; cf. Starke et al., 1989) if the release is of vesicular origin, is $[Ca^{2+}]_o$-dependent (Table 1), and is associated with axonal conduction. The ligand-gated release by nicotinic acetylcholine receptor (nAChR) or P2X receptor stimulation is also $[Ca^{2+}]_o$-dependent (Sershen et al., 1997; cf. Wonna-

cott, 1997). Because it has been shown that α_2-adrenoceptor activation (Vizi et al., 1995b) inhibits the release of NE evoked by nAChR stimulation, it seems very likely that this type of release is subjected to presynaptic inhibition.

There is a $[Ca^{2+}]_o$-independent release that is not associated with neuronal conduction and not of vesicular origin. It has been reported that transmitters can be released by drugs (e.g., ouabain, indirectly acting sympathomimetic amines) or conditions (e.g., ischemia) in the absence of $[Ca^{2+}]_o$ (cf. Ádam-Vizi, 1992; Bernáth, 1992), which has been attributed to an increase in intracellular Na^+ concentration ($[Na^+]_i$; Vizi, 1972; Baker and Crawford, 1975; Erulkar and Rahamimoff, 1978; Schoffelmeer and Mulder, 1983). This type of release is not subject to presynaptic modulation (Vizi, 1984) and is carried out by reversed operation of the plasma membrane transporter mediated via an increase in $[Na^+]_i$ (Table 1). The carrier-mediated release (Vizi, 1972, 1978; Vizi et al., 1985; Kauppinenen et al., 1988; Pin and Bockaert, 1989; Attwell et al., 1993; Levi and Raiteri, 1993; Milusheva et al., 1994, 1996; Malva et al., 1998a,b; cf. Vizi and Kiss, 1998) does not require energy and is consistent with a drop in intracellular ATP levels and the consequent inhibition of Na^+,K^+-activated ATPase activity, which leads to a decline in the Na^+ electrochemical gradient across the plasma membrane and accumulation of $[Na^+]_i$ (Nicholls and Attwell, 1990). The excessive transmitter release of nonvesicular origin (Attwell et al., 1993) cannot be modulated via presynaptic receptors (Table 1). A similar mechanism is responsible for $[Ca^{2+}]_o$-independent release of different transmitters during ischemia simulated by oxygen and glucose withdrawal (Kauppinenen et al., 1988; Budd, 1998).

K^+ excess has been used for a long time to study transmitter release. It is $[Ca^{2+}]_o$-dependent and is likely to be of vesicular origin (Table 1), at least at low concentrations.

The overwhelming majority of the evidence for presynaptic receptor-mediated modulation of transmitter release derives from assays of agonist- and antagonist-induced changes in the release rate from in vitro (slice, synaptosomes) and in vivo (microdialysis, amperometry) preparations. Although assay of the amount of transmitters in the superfusate or in the dialysate is limited in spatial and temporal resolution, electrophysiological methods (e.g., whole-cell recording) in brain slices or in

TABLE 1
Characteristics of different types of transmitter release

	Subject to Presynaptic Modulation	$[Ca^{2+}]_o$-Dependent	Mode of Release	Ca^{2+} Channel Involved	TTX-Sensitive	Carrier Involved
Neuronal frequency-coded	Yes	Yes	Vesicular exocytosis	Yes	Yes	No
Ligand-gated	Yes	Yes	Vesicular exocytosis	Yes	Yes	No
Carrier-mediated	No	No	Cytoplasmic	No	Yes/no	Yes
$[K^+]_o$ excess	Yes/no[a]	Yes	Vesicular exocytosis	Yes	No	No

[a] At high $[K^+]_o$ (extracellular K^+ concentration) (>60 mM), there is no presynaptic modulation.

cell culture help us to overcome these problems and to study the effects of ligands on presynaptic terminals recording the postsynaptic responses. However, even the electrophysiological recordings of the frequency of spontaneous postsynaptic currents or the amplitude of the evoked postsynaptic current, without a change in postsynaptic sensitivity to the synaptic transmitter, provide convincing evidence that the receptor in the study is expressed on the terminal. This technique fails to exclude the possibility that a chemical is released from the postsynaptic site that may act retrogradely, affecting the release of transmitter from the presynaptic site. Therefore, to circumvent these difficulties, the final conclusion should be drawn from data obtained from different techniques.

1. Heteroreceptor-Mediated Control of Transmitter Release. An important consequence of the expression of receptors on axon terminals is the capability of modulation (increase or decrease) of transmitter release triggered by the action potentials when they invade presynaptic terminals. Heteroreceptors are located presynaptically; they bind transmitters other than those released by the axon terminal on which they reside. Heteroreceptors can be ionotropic or metabotropic.

The first neurochemical and pharmacological evidence of heteroreceptors was obtained when it was shown in guinea pig ileal longitudinal muscle strip preparation that the stimulation-evoked release of ACh from the Auerbach plexus is tonically controlled by NE released from the neighboring noradrenergic neurons via α-adrenoceptors (Vizi, 1968; Paton and Vizi, 1969; Vizi and Knoll, 1971). Although NE or epinephrine inhibited the release of ACh in a concentration-dependent manner, phenylephrine did not affect it. The release in response to axonal stimulation was increased when the α-adrenoceptor antagonist phentolamine was present, indicating that the release was tonically controlled by endogenous NE. This was the first indication of inhomogeneity of α-adrenoceptors; NE and phenylephrine, two α-adrenoceptor agonists, have different effects on ACh release. Today, they are designated α_2- and α_1-adrenoceptors. Also, the stimulation-evoked release of NE from sympathetic nerve in the heart is inhibited by ACh released from the vagal nerve (Lindmar et al., 1968; Löffelholz and Muscholl, 1969a). These two observations provided the first evidence for presynaptic interactions between neurons by means of their transmitters, via heteroreceptors. The main difference between these two effects is that in the Auerbach plexus, there is no synaptic contact between noradrenergic and cholinergic axon terminals (Gordon-Weeks, 1982), but still there is a functional connection; stimulation of a noradrenergic axon results in an inhibition of ACh release (Vizi and Knoll, 1971; Manber and Gershon, 1979), whereas in the heart, vagal nerve endings make synaptic contacts with the noradrenergic axon terminals (Ehinger et al., 1970).

Interaction via heteroreceptors (α_{2A}, α_{2B}, M2, μ, and so on) located on varicosities has been shown (cf. Vizi, 1979; Starke, 1981; Starke et al., 1989; Göthert and Schlicker, 1991) between different axon terminals in different neurons (Table 2). Because the amount of transmitters released depends on the magnitude and duration of terminal depolarization and on Ca^{2+} influx, ionotropic heteroreceptors that depolarize and/or increase Ca^{2+} influx increase the release. In contrast, metabotropic heteroreceptors that enhance K^+ or Cl^- conductance and are coupled to G proteins reduce the release. This type of presynaptic modulation is graded. Only axodendritic axosomatic and dendrodendritic synaptic or nonsynaptic interactions regulate the generation of an action potential.

2. Autoreceptor-Mediated Control of Transmitter Release. The first evidence was provided in the 1970s when Starke (1971) and others (De Potter and Chubb, 1971; Farnebo and Hamberger, 1971a; Kirpekar and Puig, 1971) showed that NE inhibits its own release via α-adrenoceptors. Later, it turned out that these receptors are different from those located on the postsynaptic site. Therefore, presynaptic α-adrenoceptors have been named α_2-adrenoceptors (Langer, 1977, 1981a,b).

The notion that the release of NE (Starke, 1971; Langer, 1974; Stjärne, 1981, 1989), and other transmitters (Langer, 1974; Starke, 1977; Westfall, 1977; Vizi, 1979, 1984a; Starke et al., 1989; Kalsner and Westfall, 1990; Vizi and Lábos, 1991; Kilbinger et al., 1993; Göthert and Schlicker, 1997; Vizi and Kiss, 1998) can be modulated via stimulation of presynaptic autoreceptors (α_2, M2, μ, and so on) sensitive to transmitter released from axon terminal on which the receptor is expressed is now widely accepted (Table 2). This can be envisaged as an attempt to limit the release of excessive amounts of transmitter to keep postsynaptic responses within the physiological range.

3. Presynaptic Ionotropic Receptors. Recent convergence of data from morphological and functional (pharmacological, neurochemical, and electrophysiological) studies provided new insights into the role of presynaptic ligand-gated ion channels (cf. McGehee and Role, 1996; MacDermott et al., 1999) in modulation of transmitter release, thereby in the efficacy of synaptic and nonsynaptic communication. Activation of ionotropic receptors results in very rapid changes of ion channels.

a. Nicotinic Acetylcholine Receptors. Several lines of neurochemical, pharmacological, morphological, and electrophysiological evidence indicate that in the CNS, nAChRs are mainly involved in presynaptic modulation of transmitter release and are not receptors of postsynaptic localization transmitting cholinergic messages (Wonnacott et al., 1989, 1995; cf. McGehee et al., 1995; Vizi et al., 1995; McGehee and Role, 1996; Sershen et al., 1997; Wonnacott, 1997; Vizi and Kiss, 1998). Activation of nAChRs in brain regions either results in a transmitter release or facilitates the release due to axonal stim-

TABLE 2

References for the effect of stimulation of presynaptic receptor (ionotropic and metabotropic) activation by major transmitters and ATP (adenosine) on $[Ca^{2+}]_o$-dependent transmitter release in the CNS [neurochemical and electrophysiological (EP) evidence]

	Increase of Release		Inhibition of Release	
	Via Autoreceptors	Via Heteroreceptors	Via Autoreceptors	Via Heteroreceptors
Glutamatergic (Glu)	AMPA,[4] NMDA,[46] KA[49]	nAChR (α7),[17] P2X,[34] A$_{2A}$,[36] GABA$_A$[53]	mGluR$_{4/7/8 \text{ (EP)}}$,[6] KA[5]	GABA$_B$,[15] M2 (EP),[18] A$_1$,[48] α_2[52]
GABAergic (GABA)		D$_1$,[3] nAChR (α7 or $\alpha4\beta2$, EP),[1] 5 HT$_3$ (EP)[21]	GABA$_B$[10]	mGluR$_{2/3 \text{ (EP)}}$,[19] KA,[16] M2,[26] D$_2$,[32] 5HT$_{1A}$ (EP),[20] A$_{2A}$ (EP)[51]
Cholinergic (ACh)	nAChR[9]	A$_{2A}$,[37] P2X[38]	M2,[8] M4[7]	5-HT$_{1B}$,[22] A$_1$ (EP),[35] D$_2$,[42] A$_1$[43]
Noradrenergic (NE)	α_1[11]	NMDA[23]/AMPA/KA,[24] nAChR($\alpha3\beta2$),[2] GABA$_A$,[25] P2X,[40] 5-HT$_3$[57]	α_{2A}[12]	GABA$_B$,[25] P2Y,[39] A$_1$[50]
Serotonergic (5-HT)	5-HT$_3$[55]	AMPA[27]	5-HT$_{1B/D}$,[13,14] 5-HT$_{1D}$[54]	α_{2A},[30] GABA$_A$,[28] GABA$_B$,[29] M1[31]
Dopaminergic (DA)		P2X,[41] non-NMDA,[44] nAChR ($\alpha4\beta2$,[45] $\alpha3\beta2$[47]), 5-HT$_3$[56]	D$_2$[33]	

[1] (α7, EP) Alkondon et al., 1996, 1997. ($\alpha4\beta2$, EP) Lu et al., 1998; Lena and Changeux, 1997.
[2] ($\alpha3\beta2$) Vizi et al., 1995; Sershen et al., 1997.
[3] (D$_1$) Floran et al., 1990.
[4] (AMPA) Barnes et al., 1994; Chaki et al., 1998.
[5] (KA) Chittajallu et al., 1996.
[6] [mGluR$_{4/7/8}$ (EP)] Scanziani et al., 1997.
[7] (M4) McKinney et al., 1993.
[8] (M2) Richards, 1990.
[9] (nAChR) Wilkie et al., 1996.
[10] (GABA$_B$) Pittaluga et al., 1987.
[11] (α_1) Pastor et al., 1996.
[12] (α_{2A}) Kiss et al., 1995; and see Table 3.
[13] (5-HT$_{1B/D}$) Maura et al., 1986.
[14] (5-HT$_{1B/D}$) Limberger et al., 1991; Jackisch et al., 1999a.
[15] (GABA$_B$) Pende et al., 1993.
[16] (KA) Cunha et al., 1997.
[17] (α7) Gray et al., 1996.
[18] (M2) Marchi and Raiteri, 1989; (EP) Hasselmo and Bower, 1992.
[19] [mGluR$_{2/3}$ (EP)] Poncer et al., 1995.
[20] [5-HT$_{1A}$ (EP)] Bijak and Misgeld, 1997.
[21] [5-HT$_3$ (EP)] Peters et al., 1992; Piguet and Galvan, 1994.
[22] (5-HT$_{1B}$) Maura and Raiteri, 1986.
[23] (NMDA) Pittaluga and Raiteri, 1990.
[24] (AMPA/KA) Pittaluga and Raiteri, 1992a; Desai et al., 1994, 1995; Patel and Croucher, 1997; Cowen and Beart, 1998.
[25] (GABA$_B$) Fung and Fillenz, 1983.
[26] (M2) Raiteri et al., 1990b; (EP) Levey et al., 1995.
[27] (AMPA) Pittaluga et al., 1997.
[28] (GABA$_A$) Balfour, 1980.
[29] (GABA$_B$) Andrews et al., 1992.
[30] (α_{2A}) Gobbi et al., 1990; MacDonald et al., 1997.
[31] (M1) Marchi et al., 1986.
[32] (D$_2$) Floran et al., 1997; Hársing and Zigmond, 1997.
[33] (D$_2$) Hoffmann and Cubeddu, 1984.
[34] (P2X) Gu and MacDermott, 1997.
[35] (A$_1$) Morton and Davies, 1997.
[36] (A$_{2A}$) Popoli et al., 1995.
[37] (A$_{2A}$) Cunha et al., 1994, 1995; Brown et al., 1990.
[38] (P2X) Sperlágh and Vizi, 1991; Sun and Stanley, 1996.
[39] (P2Y) von Kugelgen et al., 1994; Koch et al., 1997.
[40] (P2X) Boehm, 1999.
[41] (P2X) Zhang et al., 1996.
[42] (D$_2$) Hoffmann and Cubeddu, 1984.
[43] (D$_2$) Cunha et al., 1994; Jackisch et al., 1984.
[44] (non-NMDA) Petitet et al., 1995.
[45] (nAChR, $\alpha4\beta2$) Grady et al., 1994.
[46] (NMDA) Montague et al., 1994 (via NO production).
[47] (nAChR, $\alpha3\beta2$) Kulak et al., 1997.
[48] (A$_1$) Corradetti et al., 1984; Fastbom and Fredholm, 1985.
[49] (KA) Terrian et al., 1991; Malva et al., 1996.
[50] (A$_1$) Harms et al., 1978; von Kügelgen et al., 1992.
[51] (A$_{2A}$) Kirk and Richardson, 1994; (EP) Mori et al., 1996.
[52] (α_2) Kamisaki et al., 1992; Bickler and Hansen, 1996.
[53] (GABA$_A$) Herrero et al., 1999.
[54] (5-HT$_{1D}$) Galzin et al., 1992 (human); Maura et al., 1993 (human).
[55] (5-HT$_3$) Martin et al., 1992; Bagdy et al., 1998.
[56] (5-HT$_3$) Zazpe et al., 1994.
[57] (5-HT$_3$) Allgaier et al., 1995.

ulation (cf. MacDermott et al., 1999; Vizi and Lendvai, 1999). ACh increases ACh via nACh autoreceptors (Marchi et al., 1999) and Glu, NE, 5-HT, γ-aminobutyric acid (GABA), and DA release via nACh heteroreceptors (cf. Wonnacott, 1997; Vizi and Lendvai, 1999). Lena et al. (1993) suggested that presynaptic nAChRs, depending on their apparent localization, may differentially influence the release of transmitter that is associated with nerve conduction and that is not resulted from axonal conduction. The release of NE from the hippocampal slices (Vizi et al., 1995; Sershen et al., 1997) and DA from striatal slices (Marshall et al., 1996) evoked by

nAChR activation is tetrodotoxin- and mecamylamine-sensitive and $[Ca^{2+}]_o$-dependent (Sershen et al., 1997; cf. Vizi and Lendvai, 1999). In contrast, the release from synaptosomal preparation (defined as presynaptic elements) in nAChR stimulation was tetrodotoxin(TTX)-insensitive (Clarke and Reuben, 1996). The TTX sensitivity of nAChRs-evoked transmitter release has been interpreted as "preterminal" rather than presynaptic location of nAChRs (Wonnacott, 1997). This would indicate that the nAChRs are expressed on the preterminal axon and that their activation elicits an action potential that consequently opens voltage-dependent Ca^{2+} channels in the terminal to release transmitter. A more convincing explanation is that nAChRs are expressed on the boutons and their activation results in depolarization and Ca^{2+} influx (for review, see MacDermott et al., 1999; Vizi and Lendvai, 1999). Presynaptic nAChRs are likely to be as diverse in subunit composition as their somatodendritic counterparts (cf. Vizi and Lendvai, 1999).

An important question arises as to whether presynaptic nAChRs could be targeted by endogenously released ACh, which is limited by fast enzymatic hydrolysis, or whether they are silent receptors that are activated only during smoking or cholinesterase inhibition. Taking into account the diffuse cholinergic projections and the relatively low proportion of cholinergic boutons making synaptic contact (7–14%) in the CNS (Descarries et al., 1997), it seems likely that ACh released from varicose axon terminals plays both synaptic and nonsynaptic presynaptic modulator roles. Kása et al. (1995) showed in the cortex that ACh could be released even from nonsynaptic varicosities.

Regardless of the interaction between cholinergic terminals and noradrenergic, dopaminergic, and serotonergic varicosities equipped with nAChRs, the stimulation of these receptors by nicotine inhaled during smoking may result in a release of excitatory amino acids (Toth et al., 1993) and NE, DA, or 5-HT, transmitters that are able to diffuse far away from the release site as demonstrated by microdialysis studies (Schneider et al., 1994) and affect tonically the release of other transmitters or the firing rate of other circuitry.

b. Glutamate Receptors (N-Methyl-D-aspartic Acid, α-Amino-3-hydroxy-5-methysoxazole-4-propionic Acid, and Kainate Receptors). The vast majority of excitatory synapses are glutamatergic, in which Glu transmits the signal through postsynaptic ionotropic [*N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methysoxazole-4-propionic acid (AMPA), and kainate (KA)] and metabotropic receptors (Bettler and Mulle, 1995). Glu is a fast excitatory transmitter in the CNS and has been shown, with GABA, to interact primarily with receptors in the synaptic cleft (Tong and Jahr, 1994; Geiger et al., 1997; Jensen et al., 1998; Dingledine et al., 1999; MacDermott et al., 1999).

There are several reports of presynaptic localization of GluRs and their involvement in transmitter release (Table 2). The fact that NMDA releases Glu (Pittaluga et al., 1996), DA (Kuo et al., 1998), and NE (Pittaluga and Raiteri, 1996) from axon terminals indicates that Glu released is able to facilitate transmitter release via NMDA receptors. In addition, presynaptic AMPA receptor activation results in an increase of Glu release, provided that the receptor's fast desensitization was prevented by cyclothiazide (Barnes et al., 1994; Desai et al., 1994). However, Montague et al. (1994) hinted that there is some doubt regarding this conclusion. They showed that Glu and NE release from cortical synaptosomes was in correlation with NMDA-induced production of nitric oxide (NO), an endogenous chemical that is able to inhibit basal membrane transporters, thereby increasing the concentration and life-span of transmitters (e.g., Glu and NE) released into the extracellular space. The inhibition of neuronal NO synthase by 7-nitroindazole protects against NMDA-mediated excitotoxic lesions but not against those evoked by AMPA or KA (Schulz et al., 1995).

It has also been shown that KA and Glu can reduce Glu release via a presynaptic receptor that controls chloride channels (Sarantis et al., 1988). In the presence of uptake inhibitors, even Glu (Asztely et al., 1997; Kullman and Asztely, 1998) and GABA (Isaacson et al., 1993) may have extrasynaptic actions. Until now, there has been no convincing evidence for the nonsynaptic release of Glu. In the synapse, an active transport mechanism limits the intrasynaptic concentration of Glu (cf. Gelagashvili and Schousboe, 1998).

In addition, it has been shown that presynaptic AMPA receptors (cf. Tarnawa and Vizi, 1998) play a role in the regulation of the release of neurotransmitters in several brain areas. Activation of AMPA receptors releases NE from nerve terminals. GYKI 52466 [1-(4-aminophenyl)-4-methyl-7,8-methylene-dioxy-5*H*-2,3-benzodiazepine], a non-NMDA receptor antagonist (cf. Vizi et al., 1996, 1997), blocked aspartate release from forebrain slices, Glu release from cerebellar cultures and hippocampal synaptosomes, and DA release from rat mesencephalic cultures evoked by AMPA receptor stimulation. The release of DA from nigrostriatal axon terminals in the striatum is also increased by stimulation of NMDA and non-NMDA receptors (Kuo et al., 1998; for a review, see Morari et al., 1998). These data provide increasing support for the conclusion that NMDA and non-NMDA receptors (AMPA and KA) are located on presynaptic nerve terminals and are able to influence transmitter release (MacDermott et al., 1999).

c. γ-Aminobutyric Acid_A Receptors. Frank and Fuortes (1951) were the first to show that the inhibition of excitatory postsynaptic potentials in motoneurons is a presynaptic event. Several reports (Kardos, 1999) have shown that most of the physiological actions of GABA are mediated via GABA_A (Seabrook et al., 1997; Sieghart et al., 1999; Vizi and Sperlágh, 1999; Whiting,

1999), and these receptors (Barnard et al., 1998) are involved in the presynaptic inhibition of signal transmission in, for example, the hippocampus (Vautrin et al., 1994) and feline spinal motoneurons (Stuart and Redman, 1992). These effects are mediated via a rapid increase of chloride-dependent conductance (cf. Mody et al., 1994; Vautrin et al., 1994). Phasic and tonic types of $GABA_A$ receptor-mediated inhibition have been described in cerebellar granule cells (Brickley et al., 1996; cf. Nusser et al., 1998). These cells, however, receive GABAergic input only from a single cell type (Golgi cells). Nevertheless, Nusser et al. (1998) showed that exclusive extrasynaptic presence of the δ-subunit-expressing $GABA_A$ receptors suggests that tonic inhibition could be mediated mainly by nonsynaptic $\alpha6\beta2/3\delta$ receptors, whereas phasic inhibition is due to the stimulation of intrasynaptic $GABA_A$ receptors. It has been shown (Herrero et al., 1999) that $GABA_A$ receptor activation by GABA reduces and increases Glu release from cortical neurons in culture, depending on the membrane potential.

d. 5-Hydroxytryptamine₃ Receptors. 5-HT_3 receptors have a much lower affinity than 5-HT_1 receptors (Hoyer, 1990) and have a high density in the area postrema, the entorhinal cortex, and the amygdala (Kilpatrick et al., 1990), indicating their role in transmission. The activation of 5-HT_3 receptors makes the membrane permeable to Na^+ and K^+ and mostly impermeable to divalent cations. 5-HT_3 receptor antagonists possess medical applications as antiemetics, anxiolytics, and antipsychotics (cf. Göthert and Schlicker, 1997).

Electrophysiological evidence was obtained that the stimulation of 5-HT_3 receptors leads to the increased release of GABA (cf. Peters et al., 1992; Piguet and Galvan, 1994), DA (Zazpe et al., 1994), 5-HT (Martin et al., 1992; Bagdy et al., 1998), and NE (Allgaier et al.,1995).

e. P2X Receptors. Extracellular ATP acts as a signal transmitter through P2X receptors, which are ligand-gated ion channels, with a significant permeability to Ca^{2+}, Na^+, and K^+ (cf. Bean, 1992; Ralevic and Burnstock, 1998). These receptors are distributed throughout the body, including synapses where ATP is able to transmit signals (cf. Sperlágh and Vizi, 1996; Sperlágh et al., 1997, 1998; Khakh and Kennedy, 1998). Their locations could be presynaptic and postsynaptic. P2X receptors are also known for their high Ca^{2+} permeability (Rogers et al., 1997) and capacity to increase transmitter release from nerve terminals (ACh: Sperlágh and Vizi, 1991; Sun and Stanley, 1996; Glu: Gu and MacDermott, 1997; Khakh and Henderson, 1998; DA: Zhang et al., 1996; NE: Boehm, 1999).

4. Presynaptic Metabotropic Receptors. The activation of membrane receptors expressed in the membrane is a common mechanism through which cellular functions, including neurotransmitter release, can be modulated (Table 2). Metabotropic receptors are coupled to G pro-

teins. The latter are proteins (containing α-, β-, and γ-subunits) that are present in membranes of the cell and transduce the receptor activation event to changes in enzyme or ion-channel activity.

a. α_2-Adrenoceptors. It is clear from their structure and pharmacology that α_2-adrenoceptors belong to the G protein-linked family and, in most cell types, are coupled to PTX-sensitive G proteins. It is well established that some receptors inhibit adenylyl cyclase through the G protein G_i. The activation of α_2-adrenoceptor subtype has been shown to inhibit adenylyl cyclase activity, decrease cAMP levels, and inhibit Ca^{2+} channels in many cell types, including neurons. cAMP has a facilitatory effect on many transmitter systems, including the noradrenergic system (Majewski et al., 1990). Therefore, it has been suggested that α_2-adrenoceptors may inhibit transmitter release (e.g., NE) by inhibiting adenylyl cyclase (Schoffelmeer et al., 1986).

Pharmacologically, four subtypes of the α_2-adrenoceptor have been identified: α_{2A}, α_{2B}, α_{2C}, and α_{2D} (Bylund et al., 1988a,b; Bylund et al., 1991, 1992, 1994; Deupree et al., 1996). Genetically, α_{2A} and α_{2D} subtypes were shown as orthologs, with the α_{2A} being present in humans (Bylund et al., 1988a, 1991), pig, and rabbit. Table 3 shows the presynaptic localization of different subtypes of α_2-adrenoceptors. It is interesting to note that the α_{2B} subtype of autoreceptors is mainly located in varicosities of noradrenergic terminals in the periphery and that α_{2A} is mainly located in the CNS. Both subtypes are involved in autoregulation of NE release. The heteroreceptors expressed on varicosities synthesizing ACh and 5-HT are of the α_{2A} subtype (Table 3).

Presynaptic inhibitory α_2-adrenoceptors are present on serotonergic nerve endings of the human neocortex (Raiteri et al., 1990a; Grijalba et al., 1996), and endogenous NE is able to control the release of 5-HT from human and rat neocortex (Feuerstein et al., 1993).

b. Dopamine Receptors (D_1, D_2). DA receptors are divided into two families designated D_1 and D_2. D_1 receptors activate G_s proteins, and D_2 receptors activate G_i proteins (cf. Missale et al., 1998). Stimulation of D_2 receptors results in the inhibition of the release of DA from dopaminergic nerves (Hársing and Zigmond, 1997). Activation of these presynaptic receptors inhibits the release from their respective nerve terminals of other neurotransmitters, such as NE, ACh, and GABA (Hársing and Zigmond, 1997), from the striatum. Although D_2 receptors are coupled to inhibition of adenylyl cyclase in some cell types (Onali et al., 1985), this pathway is unlikely to be involved in the autoinhibition of DA release (cf. Starke et al., 1989), because forskolin failed to affect D_2 receptor-mediated inhibition (Bowyer and Weiner, 1989). Evidence was obtained that DA receptors and transporters are located at more remote sites (Smiley et al., 1994; Nirenberg et al., 1996, 1997). The stimulation of D_1 receptors increases Ca^{2+} influx (cf. Missale

TABLE 3
Subtypes of presynaptic auto- and hetero-α_2-adrenoceptors expressed on axon terminals and on locus ceruleus
For expression of mRNA of α_2-adrenoceptor subtypes, see Winzer-Sershan et al. (1997a,b).

	Subtype		Reference
Heteroceptor			
Cholinergic			
Ileum (guinea-pig Auerbach plexus)	α_{2A}		Blandizzi et al., 1991, 1993
Serotonergic			
Synaptosome (rat brain)	α_{2A}		Gobbi et al., 1990
Autoreceptor			
Noradrenergic			
Ileum (guinea pig)		α_{2B}	Blandizzi et al., 1993
Thymus (rat)		α_{2B}	Haskó et al., 1995
Spleen (rat)		α_{2B}	Elenkov and Vizi, 1991
Heart (guinea pig)		α_{2B}	Vizi ES (unpublished)
(human)		α_{2B}	Vizi and Lendvai, 1997; Sato et al., 1999
Hippocampus (rat)	α_{2A}		Kiss et al., 1995
Hypothalamus (rat)	α_{2A}		Karkanias and Etgen, 1993; Sperlágh et al., 1998
Cortex (rat)	α_{2A}		Trendelenburg et al., 1993, 1994
(human)	α_{2A}		Raiteri et al., 1992; Sastre and Garcia-Sevilla, 1994a,b; Garcia-Sevilla et al., 1999
Spinal cord (rat)	α_{2A}		Umeda et al., 1997
(human)	α_{2A}		Lawhead et al., 1992
Synaptosome (rat brain; rat)	α_{2A}		Gobbi et al., 1990
Locus ceruleus (rat)	α_{2A}		Mateo et al., 1998
Arteries (human gastric and ilecolic)	α_{2A}		Guimaraes et al., 1998

et al., 1998) and increases GABA release from the striatum (Floran et al., 1990; Hársing and Zigmond, 1997).

c. Muscarinic Receptors (M1, M2). There are at least three muscarinic receptor subtypes (M1, M2, and M3) involved in the modulation of transmitter release (Starke et al., 1989; Raiteri et al., 1990c; Caulfield, 1993; Caulfield and Birdsall, 1998). This receptor diversity may to some extent explain the diverse range of signal transduction mechanisms; these include inhibition of Ca^{2+} influx (Allen and Brown, 1993; 1996) and adenylyl cyclase, stimulation of guanylyl cyclase, activation of phospholipase C, and direct inhibition of Ca^{2+} channels and activation of K^+ channels (cf. Felder, 1995). There is reasonably good evidence that the M2 (M4) receptors expressed on cholinergic (Lapshak et al., 1989; Quirion et al., 1995; Allen and Brown, 1996) and noradrenergic varicosities play a physiologically important role in the modulation of transmitter release.

The muscarinic receptors that inhibit NE release appear to be of the M2 subtype in the periphery and CNS (cf. Raiteri et al., 1990), but there is no such a modulation in the hippocampus (Milusheva et al., 1994; Jackisch et al., 1999b). The stimulation-evoked release of NE from hippocampal slices is not modulated by muscarinic receptors, because noradrenergic boutons are not equipped with muscarinic receptors (Milusheva et al., 1994; Jackisch et al., 1999b). In contrast, there are muscarinic receptors, apparently of the M1 subtype, that increase the release of NE (North et al., 1985; Raiteri et al., 1990c) expressed on noradrenergic axon terminals in the periphery. The M_1 receptor is generally coupled to PTX-insensitive G protein. Its activation results in formation of inositol trisphosphate and diacylglycerol. In contrast, the M2 receptor is coupled via PTX-sensitive G protein to the N-type Ca^{2+} channel (Hille, 1992). The role of M4 in "negative feedback" modulation (McKinney

et al., 1993) has been questioned by the finding that after a selective lesion of the fimbria fornix there was a loss in M2 but an increase in M4 receptors (Wall et al., 1994). The relative importance of these inhibitory and stimulatory muscarinic receptors may vary in noradrenergic neurons from different locations.

d. 5-Hydroxytryptamine Receptors. The pharmacology of 5-HT receptors has made tremendous progress in the past decade. Although more than 14 identified receptors have been discovered (cf. Hoyer et al., 1994; Murphy et al., 1999), only a few selective receptor agonists or antagonists are available. It is generally accepted that $[Ca^{2+}]_o$-dependent release of 5-HT from neurons originated from brainstem raphe nuclei (Törk, 1990) can be modulated by presynaptic autoreceptors (cf. Göthert and Schlicker, 1997) and heteroreceptors (cf. Göthert and Schlicker, 1991). Evidence for inhibitory presynaptic 5-HT autoreceptor was shown first by Farnebo and Hamberger (1971b). The serotonin autoreceptors have been classified as $5-HT_{1B/D}$ (Engel et al., 1986; Maura and Raiteri, 1986). In guinea pig hippocampal slice, the release of 5-HT is modulated via $5-HT_{1D}$ autoreceptors, as in humans (Maura et al., 1993; Galzin et al., 1995), whereas they are of the $5-HT_{1B}$ subtype in rats. Activation of these receptors results in a decrease of 5-HT release evoked by axonal stimulation (Maura and Raiteri, 1986; Limberger et al., 1991).

$5-HT_{1A}$ receptors, which are also called autoreceptors, are expressed on the soma and dendrites of the neurons of the raphe nucleus. Their activation inhibits the firing rate of the serotonergic fibers and their desensitization after long-term treatment with 5-HT uptake blocker restores action potential firing. Therefore, the $5-HT_{1A}$ receptor plays an important role in the effect of antidepressants (Mongeau et al., 1997). $5-HT_{1A}$ knockout mice

had elevated anxiety as a consequence of increased 5-HT release (cf. Murphy et al., 1999).

e. Metabotropic Glutamate Receptors. The presence of G protein-coupled glutamate receptors (metabotropic Glu receptors) has been described, and since 1991 (cf. Conn and Pin, 1997), eight receptors have been discovered and classified into three groups based on their linkage to second messenger systems and their pharmacology: group I acts via the phosphoinositol system, and groups II and III inhibit adenylyl cyclase. In addition, the stimulation of receptors of these three groups directly influences voltage-gated Ca^{2+} and K^+ channels through their G proteins, but their physiological correlate has not yet defined.

In a calyx-type nerve terminal in the brain stem (Takahashi et al., 1996), the activation of metabotropic Glu receptors has been observed to inhibit Ca^{2+} currents, rather than activation of presynaptic K^+ currents, and is responsible for presynaptic inhibition of transmitter release. Glu and quisqualate inhibit neuronal Ca^{2+} currents via a G protein-linked mechanism (Lester and Jahr, 1990), and this action may provide negative feedback control of Glu release (Terrian et al., 1991; Barnes et al., 1994; Malva et al., 1996).

f. γ-Aminobutyric Acid_B Receptors. The metabotropic $GABA_B$ receptors are widely distributed in the CNS, where they are located (Bowery, 1993; Billinton et al., 1999) at both presynaptic and postsynaptic locales (Billinton et al., 1999), inhibiting the presynaptic release of neurotransmitters (see Table 2) and the postsynaptic activity of certain K^+ channels (cf. Misgeld et al., 1995). The activation of presynaptic $GABA_B$ receptors is long-lasting, being mediated through G protein-coupled processes (cf. Mody et al., 1994), and results in an inhibition of Ca^{2+} and activation of K^+ conductances (Bowery, 1993; Billinton et al., 1999). $GABA_B$ receptors may influence K^+ channels through a physical coupling to the channel, but this effect is not mediated via a G protein intermediate (cf. Schousboe, 1999). The two isoforms (GBR1a and GBR1b) of $GABA_B$ receptors seem to be associated with presynaptic and postsynaptic elements in rat and human cerebellum (Billinton et al., 1999).

g. Adenosine A_1 Receptors. Adenosine inhibits the evoked release of many neurotransmitters, both from peripheral nerves and in the CNS (see Table 2). The inhibitory effect of adenosine on NE (Fredholm, 1976; Fredholm and Dunwiddie, 1988) and ACh (Vizi and Knoll, 1976; Sperlágh et al., 1997) release has been particularly well described and proved to be mediated by adenosine A_1 receptors. Adenosine A_1 receptors have the general structure expected of G protein-linked receptors, and there is evidence that G_i proteins are involved in the inhibitory effects of adenosine on neurotransmitter release, inhibiting cAMP production and N-type Ca^{2+} channels and activating K^+ permeability. In addition, there is some evidence that the activation of high-affinity adenosine A_{2A} receptors increases the release of dif-

ferent transmitters (Glu: Gu and MacDermott, 1997; ACh: Cunha et al., 1994; DA and NE: Sebastiao and Ribeiro, 1992) and has an effect on G_s protein and subsequently increases cAMP level. In contrast, its stimulation reduces the release of GABA from the recurrent collaterals of striatopallidal neurons (Kirk and Richardson, 1994).

The basal level of adenosine (20–300 nM) in the extracellular space is able to influence the activity of the neurons that are equipped with abundant adenosine A_1 and A_{2A} receptors.

The key question is: What is the role of extracellular adenosine either released from cells (cf. Mitchell et al., 1993; Thompson et al., 1993) or decomposed from ATP (ADP and AMP: Sperlágh and Vizi, 1996), especially during ischemia? It seems that adenosine, via activation of A_1 heteroreceptors being able to inhibit the release of different transmitters in the CNS (e.g., ACh: Cunha et al., 1994), plays an important role in dampening neuronal firing in epilepsy and ischemia, and it is neuroprotective (Thompson et al., 1993).

h. P2Y Receptors. Metabotropic P2Y receptors are coupled with $G_{q/11}$, G_s, and G_i proteins (cf. Ralevic and Burnstock, 1998). The stimulation of P2Y receptors activates phospholipase C, releases intracellular Ca^{2+}, and is coupled to adenylyl cyclase (cf. Khakh and Kennedy, 1998). It has been shown that P2Y receptors are involved in the reduction of NE release from rat cortical (von Kügelgen et al., 1994) and hippocampal (Koch et al., 1997) slices.

B. Plasma Membrane Transporters. Na^+/Cl^--dependent transporters, such as DA, 5-HT, NE, GABA, glycine, taurine, proline, and betaine, are members of a large family of Na^+/Cl^--containing putative transmembrane domains (Kanner and Schuldiner, 1987; Amara and Kuhar, 1993; Lester et al., 1994; Nelson, 1998). These ion-coupled transporters are "electrogenic" and lead to conductive properties (cf. Lester et al., 1996). These transporters are different from that expressed in the membrane of vesicles (Henry et al., 1998). It is generally accepted that these high-affinity transporters located on the nerve terminals and surrounding glial cells (cf. Nelson, 1998) control the temporal and spatial concentration of transmitters released into the intrasynaptic and extrasynaptic spaces via rapid uptake into nerve terminals. For example, in tissue with dense noradrenergic and GABAergic innervation, as much as 70 to 80% of released NE (Bönisch and Brüss, 1994) and GABA (Iversen and Kelly, 1975) may be recaptured, indicating that the transporter plays an important role in setting the concentration of transmitter in the extracellular space. Thus, plasma membrane transporters maintain low intrasynaptic and extrasynaptic neurotransmitter concentrations, thereby regulating synaptic and nonsynaptic efficacy; many of the transporters have been implicated as important sites for drug actions.

1. Characteristics of Transporters.

a. Protein Kinase C Dependence. It has been suggested that protein kinase C (PKC) plays a role in acute modulation of Na^+/Cl^--coupled transporters, including GABA, DA, and 5-HT (Corey et al., 1994; Osawa et al., 1994; Zhang et al., 1997; Ramamoorthy et al., 1998). Activation of PKC by phorbol ester inhibits the uptake of GABA (Osawa et al., 1994), DA (Zhu et al., 1997), 5-HT (Qian et al., 1997; Ramamoorthy et al., 1998), and NE (Apparsundaram et al., 1998).

It has been suggested (cf. Majewski and Iannazzo, 1998) that PKC, activated by diacylglycerol and/or arachidonic acid, through presynaptic receptors (M1, angiotensin, bradykinin) or nerve depolarization is involved in the facilitation of transmitter release from neurons. Majewski and Ianazzo (1998) suggested that this facilitation is mediated by the phosphorylation of proteins involved in vesicle dynamics, although a role for ion channels cannot be ruled out. Nevertheless, taking into account recent studies (cf. Shinomura et al., 1999), it seems most likely that PKC does not directly affect the release process; more likely it blocks the uptake, thereby more transmitter remains extracellular, once transmitter has been released.

b. Voltage Dependence and Modulation by Receptors. It has been shown (Lester et al., 1994; Sonders et al., 1997; Zahniser et al., 1998) that the transporter velocity is increased by hyperpolarization of the membrane and is decreased by depolarization (Sonders et al., 1997). A possible interaction between transporter and auto- or heteroreceptors is that function of the uptake system is a voltage-dependent process and membrane potential can be influenced through receptor activation. For example, stimulation of D_2 receptors opens inwardly rectifying potassium channels, resulting in transient hyperpolarization (Lacey et al., 1987). Thus, hyperpolarization produced by stimulation of receptors expressed on varicosities may result in an increase in the velocity of the uptake process, reducing the amount of transmitter in the extracellular space. This is supported by the findings of Dickinson et al. (1998) that in genetically engineered mice ($D_2^{-/-}$), the DA transporter (DAT) function was lacking, compared with $D_2^{+/+}$ mice, and that raclopride (D_2 receptor antagonist) decreased the activity of the transporter in $D_2^{+/+}$ mice. That DAT can be modulated by D_2 autoreceptors has already been suggested (Meiergerd et al., 1993). In addition, it has been shown (Barbour et al., 1988) that at high extracellular K^+ concentrations (i.e., under conditions in which the cell is depolarized), Glu uptake is abolished (Szatkowski et al., 1990) and a marked release of Glu occurs.

Because a discrepancy was observed between transport rates and substrate-gated ion fluxes (e.g., Na^+) determined for different substrates, it was suggested (Sitte et al., 1998) that plasma membrane amine transporters operate in a channel mode. The releasing action would depend on current induced by the substrate rather than on their uptake rate. Na^+ would be the potential charge carrier, which could trigger carrier-mediated release of DA by enhancing $[Na^+]_i$ at the cytoplasmic site of the DAT (Levi and Raiteri, 1976; Liang and Rutledge, 1982; Bönisch, 1986; Yamazaki et al., 1996).

c. Temperature Dependence. The capacity of inward transport of transmitters depends on the temperature; at low temperatures, transporters fail to operate (Lindmar and Löffelholz, 1972; Asztely et al., 1997; Vizi, 1998). When the temperature is reduced from 37°C to 25°C, the DA uptake by striatal preparations results in a mild reduction in K_m and a dramatic decrease in V_{max} (Liang and Rutledge, 1982; Bonnet et al., 1990). Indeed, desipramine, an uptake blocker, fails to increase NE release in response to axonal stimulation when the temperature was reduced to 17°C (Vizi, 1998). A 10°C increase in temperature doubled the turnover rate of GAT (Schwartz and Tachibana, 1990). At a low temperature (17°C), the exocytotic release of NE, DA (Vizi, 1998), and GABA (Vizi and Sperlágh, 1999) is not affected or increased; the carrier-mediated release of different transmitters (NE, DA, GABA) evoked by ischemia or ouabain administration was completely blocked (Vizi, 1998; Toner and Stamford, 1999; Vizi and Sperlágh, 1999). This fact indicates that the carrier-mediated release of transmitters is of cytoplasmic origin.

2. Substrate Selectivity.

a. Norepinephrine Transporter. NE transporters (NETs) located in the neuronal plasma membrane mediate the removal of NE from the extracellular space (cf. Graefe and Bönisch, 1988; cf. Trendelenburg, 1991; Nelson, 1998), limiting the activation of auto- and hetero-adrenoceptors expressed on different neurons by reducing the extracellular concentration of NE and thereby the amount of NE available for diffusion. NETs also transport structurally similar molecules, including DA, tyramine, and amphetamine (Bönisch, 1986; Bönisch and Brüss, 1994). Similar to other transporters, NETs use the energy of the transmembrane Na^+ gradient to take up NE inside the neuron from the intrasynaptic and/or extrasynaptic space. The direction of transport can be reversed by inward transport of any substrate (cf. Chen and Justice, 1998). At a high frequency of stimulation, so much transmitter is being released that the transporter capacity (which has been used up) becomes fully exploited and unable to continue to clear the extracellular space.

b. Dopamine Transporter. DAT is a plasma membrane glycoprotein that reaccumulates DA released into the synaptic and extraneuronal space by varicose axon terminals and thereby regulates the lifetime of DA in the extracellular space (Amara and Kuhar, 1993; Page et al., 1998). The uptake process depends on Na^+ and Cl^-. In line with these observations using electron microscopy, it has been shown (Hoffmann et al., 1998) that DATs are not located at the synaptic density but are confined to perisynaptic areas, implying that DA dif-

fuses away from the synapse. Besides its physiological role, DAT is a pharmacological target of cocaine and amphetamine in rat (Heikkila et al., 1975a,b) and in mammalian cells transfected with human DAT (Sitte et al., 1998). In an elegant experiment, it was shown in homozygote mice (DA$^{-/-}$) that DA released from nigrostriatal varicose axon terminals into the extrasynaptic space persists at least 100 times longer than in wild-type animals and that diffusion is the only mechanism for clearance (Gainetdinov et al., 1998). Amphetamine failed to release DA from homozygote mice striatum (Giros et al., 1996). In addition, it has been shown (Giros et al., 1996) that DAT is an obligatory target of cocaine and amphetamine, because these drugs have no effect on locomotor activity or DA release and uptake in DAT knockout homozygote mice. These findings indicate that blockade of uptake allows DA released from nonsynaptic varicosities to reach a much higher concentration and to remain increased in the extracellular space for a much longer time than under conditions in which the inactivation by transporter is not inhibited.

c. Glutamate Transporter. The excitatory amino acid Glu is the most prevalent transmitter in the brain; its effect on postsynaptic receptors is limited by uptake process (Erecinska, 1987) and by diffusion of Glu from the cleft. The removal of Glu from the extracellular fluid, limitation of its action occurs by uptake and by diffusion (Tong and Jahr, 1994). This is accomplished by a transporter in the plasma membrane of both neurons and astrocytes (Brooks-Kayal et al., 1998; Gelagashvili and Schousboe, 1998). Electrophysiological evidence was obtained that the block of Glu transporters potentiates postsynaptic excitation of Glu receptors (Tong and Jahr, 1994). The cellular uptake of Glu is driven by the electrochemical gradients of Na$^+$ and K$^+$ and is accompanied by voltage and pH changes. The Glu transporter limits Glu concentration in the synapse and spillover from one synapse to another.

d. γ-Aminobutyric Acid Transporter. The role of GABA transporter is to terminate synaptic events evoked by GABA released from GABAergic terminals. GABA uptake inhibitors increase and prolong GABA$_B$ receptor-mediated transmission (Dingledine and Korn, 1985; Isaacson et al., 1993). A high-affinity transporter for GABA ($K_m = 0.01–1$ μM) has been shown in the CNS (Iversen and Kelly, 1975). Blockade of GABA uptake, which reduces the amount available for diffusion and thereby limits the remote effect of GABA, significantly enhanced the slow IPSC (Isaacson et al., 1993) that represents an extrasynaptic effect. According to Schwartz (1987), the reverse operation of the carrier can raise the GABA sufficiently high to provide extracellular concentration of transmitter to a level that would affect receptors.

e. Serotonin Transporter. The serotonin transporter is also a member of a superfamily of Na$^+$- and Cl$^-$-dependent neurotransmitter transporters, which are important targets for both drugs of abuse and antidepressant compounds (Amara and Kuhar, 1993; Blakeley et al., 1994).

5-HT transporter $-/-$ mice demonstrated a complete lack of high-affinity 5-HT uptake and have increased extracellular 5-HT levels and an increased anxiety-related behavior (cf. Murphy et al., 1999). In these transporter-deficient mice, no change in response to (+)-amphetamine was found when the locomotor stimulation was studied. In contrast, the effect of cocaine on behavior was increased (Sora et al., 1998), and the locomotor-stimulatory effect of 3,4-methylenedioxymethamphetamine (Ecstasy) was reduced.

III. Nonsynaptic Varicosities

It is well known that axons both in the CNS and in the autonomic nervous system form varicose (*boutons-en-passant*) branches. The varicose axon terminals, which in the overwhelming majority do not make synaptic contacts, are the main target of presynaptic modulation. A substance released in or diffusing to the vicinity of the axon terminal can modulate the release of the principal transmitter or that of another modulator provided the axon is equipped with sensitive receptors. Many authors (cf. Langer, 1977; cf. Starke, 1977) support the idea that presynaptic modulation is a question of secretion coupling. However, others (Alberts et al., 1981; Stjärne, 1981) suggest that mechanisms related to the failure of varicosity invasion are responsible for presynaptic inhibition. It was suggested that presynaptic inhibition is the reduction in the safety factor for terminal varicosity invasion by the axonal nerve impulse (Stjärne, 1981, 1989). The release of NE from sympathetic nerve terminals by the invading nerve impulse is a very uncertain process, with a high proportion of failures at any individual varicosity (Blakeley and Cunnane, 1979), so that any procedure marginally reducing the chance of invasion may have profound effects. Alberts et al. (1981) suggested that varicosity hillocks could control the excitability of the varicosity and the invasion of the more distal parts of the branch. The wave of depolarization arriving at the varicosity hillock reaches the firing level and generates a propagating impulse in the next intervaricose section. However, this site of action seems very unlikely because it is based on acceptance that the method of action potential conduction in a varicose terminal is similar to that in a neuron, and this is not the case. The action potential attempts to invade the whole branch without alternating depolarization with action potential generation and intervaricosital axonal conduction. The bouton is small; therefore, the action potential arriving at the first and consecutive boutons tries simply to depolarize and pass them. Although methods for analysis of the mode of impulse conduction in *boutons-en-passage* terminals are not available, it is tempting to speculate that the difference in size between the cross

section of the intervaricosital axonal part and the bouton makes it difficult for impulses to invade the whole branch. The sudden change in size of the varicose branch at the bouton might produce changes in, for example, the length constant (Vizi, 1984) and thereby influence the length of invasion of the rather lengthy arborization.

There is convincing neurochemical evidence, mainly based on studies with synaptosomal preparations and potassium-induced release, that the site of action is on the axon terminals. Therefore, there is general agreement that secretion coupling is affected by the modulators (cf. Langer, 1977; cf. Starke, 1977).

Although the axo-axonic synapse is the anatomical correlate of presynaptic modulation, convincing anatomical evidence is available that noradrenergic (cf. Oleskevich et al., 1989), serotonergic (Descarries et al., 1975; Seguela et al., 1989; Oleskevich et al., 1991), dopaminergic (Descarries et al., 1991), and cholinergic (Descarries et al., 1997) varicosities in the CNS in a rather high percentage do not make synaptic contact. A very low synaptic incidence of monoaminergic innervation has already been documented in the adult rat cortex (Descarries et al., 1975, 1977; Beaudet and Descarries, 1978; Seguela et al., 1990, 1989), hippocampus (Oleskevich et al., 1989; Daszuta et al., 1991; Umbriaco et al., 1995), dorsal horn of the spinal cord (Ridet et al., 1993), and cerebellum (Beaudet and Sotelo, 1981).

Although the incidence of nonsynaptic nerve terminals amounted to 64% for 5-HT and 57% for NE in the dorsal horn of the spinal cord (Ridet et al., 1993), in the ventral horn (Privat et al., 1988) the synaptic contacts were the predominant, indicating that nonsynaptic communication is characteristic of the dorsal horn, and low-affinity $5-HT_2$ receptors are numerous in the ventral horn but scarce in the dorsal horn (Pazos et al., 1985, Pazos and Palacios, 1985).

Recent immunoelectromicroscopic studies have revealed a low incidence (14% in the cerebral cortex, 7% in the hippocampus, and 9% in the neostriatum) of synaptic specializations of cholinergic varicosities using cholineacetyltransferase immunostaining (Descarries et al., 1997). A similar observation was made by Kása et al. (1995, 1997) in the main olfactory bulb.

Although anatomical studies reveal the presence of nonsynaptic varicosities, functional studies are required to establish the precise mode of chemical transmission.

Indeed, strong neurochemical evidence is available that nonsynaptic varicosities release transmitters. Descarries et al. (1977, 1980, 1987) demonstrated that non-

synaptic varicosities in the CNS appear to have all the apparatus normally associated with synaptic release. Subsequently, ultrastructural examination of noradrenergic varicosities in several tissues confirmed that both large and small vesicles could undergo exocytosis in the absence of structurally specialized active zones (Thureson-Klein and Stjärne, 1981; Thureson-Klein, 1983, 1984; Zhu et al., 1986). In addition, morphological evidence was provided (Buma, 1989) for exocytosis release sites that do not make synaptic contact in rat median eminence and mesencephalic central gray substance.

The hippocampus is very rich in noradrenergic innervation originating from the locus ceruleus (Loy et al., 1980). Fine varicose axons are present in every layer of the hippocampus, but the overwhelming majority of varicosities (2.1 million/mm^3) do not make synaptic contact (Table 4). This means that each varicosity, provided they are evenly distributed, may control a volume of $\sim$500 μm^3. The distance between varicosities plays an important role in setting the concentration of transmitters in the extracellular space, because the concentration of transmitter drops in a function of 3. This means that $\sim$10 μm is the average distance between each varicosity (Fig. 2), but they are not evenly distributed, indicating that there are regions in which the local concentration of transmitters could be much higher.

Descarries et al. (1977) presented evidence that like the hippocampus, the cerebral cortex has rather dense noradrenergic innervation with remarkably uniform distribution. The latter is different from that of hippocampus. The cerebral cortex contains 346 noradrenergic varicosities/mm^2 and >6000/mm^3; therefore, each varicosity may control a volume of 150.000 μm^3.

This arrangement suggests that every varicose arborization equipped with heteroreceptors may lie within 66 μm of a noradrenergic varicosity devoid of synaptic specialization (Fig. 1).

With this calculation, we anticipated that noradrenergic varicosities in the hippocampus and cortex are evenly distributed, but this is certainly not the case. Of course, the extracellular concentration of transmitters may vary from site to site and from time to time, because there is a possibility of spatial and temporal summation of transmitters released from different varicosities.

The density of serotonergic varicosities varies between 0.24 and 2 million/mm^3 (Beaudet and Sotelo, 1981; Table 4) in the cerebellar cortex.

TABLE 4
Density of varicosities in the CNS

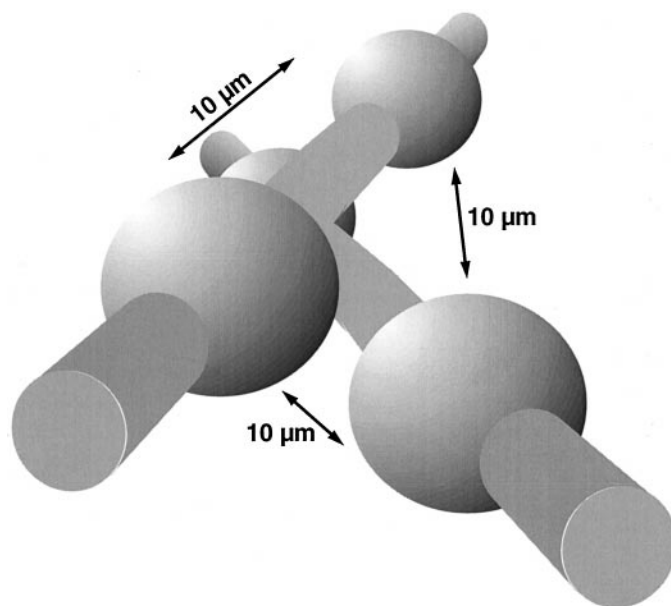| Transmitter	Location	No. of varicosities/mm^3	Reference
Noradrenergic	Hippocampus	2.1 million	Loy et al., 1990
	Cortex (cerebral)	6000	Descarries et al., 1977
Serotonergic	Cerebellar cortex	0.24 million	Beaudet and Sotelo, 1981
	Cerebellar cortex (agranular)	2 million	Beaudet and Sotelo, 1981

Fig. 2. Scheme of varicose axon terminals. The average distance between varicosities in the hippocampus is 10 μm (for details and calculations, see the text), and in the cortex, the average distance is 66 μm, provided the varicosities are evenly distributed, but this is not the case. According to Schneider et al. (1994), DA released in response to axonal activity is able to diffuse ~50 μm. This means the transmitter is released from only one varicosity; it diffuses cylindrically and the concentration drops in a function of 3. However, when the neurons fire in concert, the concentration can be much higher depending on the spatial distribution of varicosities.

IV. Extracellular Space as a Communication Channel of Nonsynaptic Interaction

Microdialysis studies show that virtually all the transmitters in the CNS are present in the extracellular space. A very important factor that determines the peak concentration of transmitter in this space is its volume accessible for the transmitter. It has been shown (Nicholson, 1985; cf. Nicholson and Rice, 1991) that this space is ~12 to 25% of the brain volume. Activity-induced changes of extracellular space in excitable tissues are a well known phenomenon. In response to neuronal

activity and in parallel with an increase in extracellular K^+ concentration, shrinkage of the extracellular space can be observed in vivo (Svoboda and Sykova, 1991; cf. Holthoff and Witte, 1998). This, in fact, can influence the concentration of transmitters released into the extracellular space.

Another important factor is the amount of transmitter released from axon terminals. A critical aspect of nonsynaptic interaction theory is that a given neuron with its numerous nonsynaptically ending varicosities (which could be a few hundred thousand!) need not, by itself, be of sufficient strength to significantly change the extraneuronal concentration of the transmitter. If that neuron is fired at the same time as a number of other neurons, their combined action may be able to increase transmitter concentration in the extracellular space to such a level that a large field will be influenced; of course, only those neurons whose terminals or dendrites are equipped with receptor sensitive to the transmitter are affected. If, in contrast, a given neuron fires asynchronously with most of the other neurons, there will be no effect on the target cell. Table 5 shows the extracellular concentration of different transmitters in the extracellular space determined by microdialysis.

Diffusion of transmitters through the extracellular space in brain slices (McBain et al., 1990) is anisotropic in both hippocampus and cortex (Nicholson and Syková, 1998), indicating some specificity. The half-life of extracellular 5-HT is 0.21 s in the substantia nigra and 0.09 s in the dorsal raphe nucleus (Bunin et al., 1998), suggesting that in the dorsal raphe nucleus, the nonsynaptic transmission is a more likely mode of communication than in the substantia nigra.

Richfield et al. (1989) succeeded in showing that there are differences in anatomical distributions and affinity states of D_1 and D_2 receptors in the rat brain. The proportion of high-affinity sites is quite different between the two subtypes. The high affinities for DA binding

TABLE 5
Concentrations of transmitters in the vesicle, synaptic cleft, and extracellular space

	Concentration	Transmitter	Location	Reference
Vesicle	90 mM	DA	Brain (rat)	Floor et al., 1995
	10 mM	NE	Hypothalamic synaptosome	West and Fillenz, 1980
	90 mM	5-HT	Dorsal raphe	Bunin and Wightman, 1998, 1999
	60–210 mM	Glu	Hippocampus	Burger et al., 1989; cf. Clements, 1996
	60 mM	ACh	Neuromuscular junction	Van der Kloot and Molgo, 1994
Synaptic cleft	6 mM	5-HT	Dorsal raphe	Bunin and Wightman, 1998
	~1 mM	ACh	Neuromuscular junction	Matthews-Bellinger and Salpeter, 1978; Kuffler and Yoshikami, 1975
	~1–5 mM	GABA	Hippocampus	Clements, 1996
	~1 mM	Glu	Hippocampus	Clements et al., 1992
Extracellular space	55 nM	5-HT	Dorsal raphe substantia nigra	Bunin and Wightman, 1998, 1999; Bunin et al., 1998
	10 μM	GABA	Hippocampus	Destexhe and Sejnowski, 1995
	0.2–0.8 μM	GABA	Hippocampus	Lerma et al., 1986
	5–55 nM	NA	Cortex	Allgaier et al., 1992
	100 nM	NA	Hippocampus	Kiss et al., 1995
	0.1–1 nM	ACh	Hippocampus	Moor et al., 1995
	3 μM	DA	Striatum	Taber and Fibiger, 1994; Benveniste and Hüttemeier, 1990
	0.1–1 μM	DA	Striatum	Kawagoe et al., 1992

to receptors in striatal slices were near 40 nM (range, 9–74 nM), and the low affinities for DA were near 2 to 4 μM.

One question regarding the cellular location of D_1 and D_2 receptors is whether they are both located on the same neuron and/or they are expressed presynaptically or postsynaptically, synaptically or nonsynaptically. For the time being, no method is available to answer these questions. It is therefore a plausible assumption that the affinity of DA for the DA receptors and the DAT and nonsynaptic DA concentration should be related to each other.

It has been speculated that the synaptic DA concentration is in the range of 10 μM and that DA is accordingly able to act on the low-affinity states of the receptors (Gonon and Buda, 1985).

The release of GABA, reaching a peak concentration of ~1 mM (Clements et al., 1992), would correspond to 3.000 to 7.500 molecules of transmitter released (Destexhe and Sejnowski, 1995). A spillover of GABA may account for differences between inhibitory responses in the hippocampus and thalamus (Destexhe and Sejnowski, 1995). It is highly probable that diffusion of transmitter between two neighboring synapses (i.e., cross-talk; Barbour and Häusser, 1997) plays an important role in long-term potentiation and long-term depression phenomena (Kullmann et al., 1996) in which associativity and cooperativity of synapses are important. This may be also involved in the activation of nearby synapses (cf. Barbour and Häusser, 1997), affecting presynaptic and postsynaptic ionotropic receptors and producing electrophysiologically detectable changes in synaptic current waveform and metabotropic receptors that may not produce a direct electrical action. However, the fact that low-affinity receptors are expressed in the synapse makes it seems likely that the cross-talk will only occasionally affect them, with the concentration of the transmitter outside the synaptic gap being much lower than that in the gap (~100 μM).

A similar observation was made with DA in the striatum (Wightman et al., 1988; Van Horne et al., 1992). DA released from the varicose axon terminals of the nigrostriatal pathway may be able to diffuse far away from release sites (Schneider et al., 1994) and inhibit the release of ACh from cholinergic interneurons. However, all of the observations made with microdialysis suggest that transmitters (NE, DA, 5-HT, and ACh) released mainly from nonsynaptic terminals are present in the extracellular space.

V. Nonsynaptically Expressed Receptors and Membrane Transporters of High Affinity as Therapeutic Targets

Many instances have been found in which the distribution of the receptors does not match the distribution of transmitter (Herkenham, 1987, 1991). Several lines of data (Table 6) indicate there are extrasynaptic receptors and transporters in different brain regions (Somogyi et

TABLE 6
Immunocytochemical localization of nonsynaptic receptors

Receptor	Location	Reference
$GABA_A$	Cerebellum	Somogyi et al., 1989
$GABA_A$	Cerebellum	Nusser et al., 1998
AMPA	Hippocampus	Baude et al., 1995
D_1, D_2	Basal ganglia	Yung et al., 1995
α_{2A}	Visual cortex	Venkatesan et al., 1996

al., 1989; Baude et al., 1995; Yung et al., 1995; Venkatesan et al., 1996; Descarries et al., 1997; Nusser et al., 1998) that are accessible for endogenous ligands. These, being located nonsynaptically, however, possess a high-affinity property and may play a physiological role in accepting chemical messages from distant neurons. Even when the synaptic and nonsynaptic receptors do not differ in affinity, however, they may be used with a different level of neuronal activity. Somogyi et al. (1989) showed in cerebellum that at a low frequency of neuronal firing, GABA released into the synaptic cleft acts at the synaptic junctions. The small amount of GABA can be removed by the transporter without reaching the extrasynaptic receptors. However, at increased excitatory input, GABA released in a much higher amount may reach remote receptors of nonsynaptic location.

In contrast, there are heteroreceptors or transporters expressed on some neurons that are not accessible by transmitters. These receptors and transporters, in addition to those previously mentioned, are of pharmacological importance because they may never reach effective concentrations of the appropriate endogenous ligands in vivo but they could be the target for drugs or they could be occupied by endogenous ligands in toxic conditions.

A. Nonsynaptic Receptors

To act effectively at a distance and at a low concentration, transmitters require high-affinity receptors (Isaacson et al., 1993). The affinity of receptors expressed in the synapse cannot be determined, because there is no method available to separate intrasynaptic and extrasynaptic receptors. Katz and Miledi (1977) showed that a low concentration of ACh has a minimal effect on the postsynaptic nAChRs, which are known to possess a low affinity for ACh (Colguhoun and Odgen, 1988). Because the intrasynaptic concentration of transmitters (see Table 5) is in the range of 0.01 to 6 mM (Kuffler and Yoshikami, 1975; Clements et al., 1992; Bunin and Wightman, 1998, 1999), the postsynaptic receptors are relatively insensitive and are of low affinity. It is therefore suggested that these receptors cannot be affected by drugs being distributed in the body in low concentrations; drugs may be able to affect these intrasynaptic receptors only at extremely high and toxic concentrations. These receptors are not targets for remote (i.e., nonsynaptic) modulation or remote signal transmission. However, there are receptors and transporters expressed on varicosities without synaptic contact that

are easily reached by endogenous substances (i.e., transmitters, modulators, and so on) and drugs (antidepressants, nicotine), and they might be affected by relatively low (0.01–1 μM) concentrations of drugs (Table 7) with a selective effect on receptors (Vizi, 1984a; Vizi and Lábos, 1991). Dense nonsynaptic localization of 5-HT$_1$ receptors was shown (Kia et al., 1996) in substantia nigra pars reticulata, where the extracellular concentration of 5-HT is 55 nM (Bunin and Wightman, 1999). Therefore, it is suggested that receptors located on varicosities without making synaptic contact seem likely to be the target for exogenous compounds (medications) acting as agonists, partial agonists, or antagonists (Vizi and Lábos, 1991). Indeed, several drugs used in clinical practice have been developed on the concept of presynaptic modulation of chemical transmission (cf. Langer, 1997; Langer et al., 1998).

B. Nonsynaptic Transporters

There are only few reports of transporter density or localization in the CNS. These data will help us to better understand the nonsynaptic interactions between neurons. It is possible that there are regions in which the density of a transporter is much lower than that in other regions; therefore, remote interaction in this region is more likely. It has been shown (Descarries et al.,1977, 1995) that labeled 5-HT and NE can be taken up from the extracellular space by varicosities without making synaptic contact. Since then, much evidence has been provided (Lester et al., 1996) that transmitter-selective transporters are expressed on nonsynaptic varicosities and are able to take up transmitters from the extracellular space, limiting the concentration of transmitter released from varicosities. Transporters regulate the lifetime of the transmitter in the extracellular space and thus the distance it can diffuse away from its release site. Therefore, the area over which a transmitter released into the extracellular space can act and the concentration of transmitter may vary from region to region, depending on the local density of transporter. It has been shown that Glu is removed from the synapse into the nerve terminal and into the glia by a low-affinity transporter (Gelagashvili and Schousboe, 1998). Similarly, the nonsynaptic and synaptic GABA transporters restrict fast GABA$_A$ receptor-mediated transmission, preventing its spillover, and spread to reach remote presynaptic GABA$_B$ receptors.

The importance of noradrenergic, serotonergic, and dopaminergic transporters has long been appreciated (e.g., the therapeutic effect of antidepressants is based on their blocking action on these transporters; cf. Barker and Blakely, 1995). Antidepressants (e.g., imipramine, fluoxetine), acting at low concentrations on nonsynaptically located membrane transporters of high affinity, are able to inhibit the uptake of NE and/or 5-HT, thereby increasing the concentration, life span, and transmission distance of the transmitter released into the microenvironment.

The diffusion of DA over long distances (a few millimeters) through a large volume of striatal tissue was observed (Doucet et al., 1986; Schneider et al., 1994) when either the nigrostriatal dopaminergic pathway was destroyed or the reuptake was inhibited. In these experiments in intact animals, DA released in response to neuronal activity diffused ~50 μm in the striatum (Schneider et al., 1994).

C. Nonsynaptic Interaction between Neurons without Receptors

Within the past few years, evidence has accumulated that NO and carbon monoxide are present in the CNS (cf. Szabó, 1996; Moncada et al., 1997) and are able to operate as signal transmitters. Nevertheless, they have not yet met all criteria necessary to be classified as transmitters. They are not synthesized in synaptic vesicles, but they are liberated as gases and then they are simply diffusing far away from their synthesis site, able to activate G proteins of remote cells and influence transporters. It has been shown that the free radical NO might play a role as an intercellular messenger in the brain (Garthwaite et al., 1988). One of the physiological functions of NO may be to prevent the uptake of different neurotransmitters. Several studies provided evidence that NO inhibits the plasma membrane transporters of different neurotransmitters. NO inhibited [^{3}H]DA (Lonart and Johnson, 1994; Pogun et al., 1994a; Cutillas et al., 1998) and [^{3}H]Glu uptake (Lonart and Johnson, 1994; Pogun et al., 1994b) but increased 5-HT uptake (Miller and Hoffman, 1994). In regard to NE uptake, according to Pogun et al. (1994a) NO had no effect, whereas Lonart and Johnson (1995a,b) reported an inhibitory effect. In all of these studies, the authors directly measured the transmitter uptake (usually in synaptosomes) in the presence of exogenously applied NO produced from different NO generators. In our study, in hippocampal slice preparation (Kiss et al., 1996), we inhibited the neuronal NO synthase, which reduced the endogenous NO production. This manipulation increased the ability of dimethylphenyl-piperazinium, an nAChR agonist, to evoke carrier-mediated release. These data suggest that endogenously produced NO is

TABLE 7
Extracellular concentration of drugs in the plasma and cerebrospinal fluid

Drug	Concentration		Reference
	Plasma	Cerebrospinal Fluid	
	μM		
Nicotine	0.4–4.5		Zevin et al., 1998
Imipramine	1–2		Besret et al., 1996
Citalopram	1		Hyttel, 1982
Desmethyl-imipramine	2	0.1	Muscettola et al., 1978
Fluoxetine	1		Pato et al., 1991

able to inhibit the operation of NE uptake carrier (at least if the direction of NE transport is reversed due to certain conditions). In addition, with the use of microdialysis, it has been shown (Kiss et al., 1999) that the systemic administration of N^{ω}-nitro-L-arginine methyl ester, an NO synthase inhibitor, significantly reduced the release of DA from the striatum (Kiss et al., 1999). It was also seen that NO synthesized in neurons by inducible NO synthase in several regions of the brain can release ACh (Ikarashi et al., 1998) and that the NO generator sodium nitroprusside (500 μM) increases extracellular DA levels in the striatum (West and Galloway, 1999) in a $[Ca^{2+}]_o$-dependent manner.

The synthesis of NO in the CNS is mainly linked to the activation of NMDA receptors by Glu. Montague et al. (1994) have shown that the activation of NMDA receptors in synaptosomal preparations from guinea pig cerebral cortex released both Glu and NE and that the release is blocked by drugs that inhibit NO production or remove NO from the extracellular space. In addition, the activation of AMPA/KA receptors also increases NO production. It is also known that the stimulation of NO production is a $[Ca^{2+}]_o$-dependent process (Garthwaite and Boulton, 1995). These findings suggest that Glu released from axon terminals increases NO production via NMDA receptor activation and is able to potentiate the release of Glu and other transmitters from the neighboring synapses. Therefore, it seems likely that NO is involved in the modulation of NMDA-induced release of neurotransmitters (Montague et al., 1994; Sandor et al., 1995; Segovia and Mora, 1998; cf. West and Galloway, 1999).

With a half-life of a few seconds, NO generated at a single point source should be able to influence function within a sphere with a diameter of ~300 to 350 μm (Garthwaite and Boulton, 1995), which is very large compared with the dimensions of a synapse. According to Gally et al. (1990), NO may diffuse up to 100 μm in 5 s. Therefore, it is suggested that NO is an ideal endogenous substance for nonsynaptic interaction and may transmit long-distance messages from transmitters (e.g., Glu) exclusively released into the synaptic gap.

VI. Clinical Implications

High-affinity transmitter receptors and transporters located nonsynaptically are the targets of many drugs of therapy and abuse. Are the receptors and transporters located outside the postsynaptic density of the synapse functionally part of a single synapse? Taking into account the morphology of arborization of noradrenergic, dopaminergic, serotonergic, and cholinergic systems, the answer is certainly no. These receptors and transporters, having no synaptic arrangements, are promiscuous and accessible to chemicals released from numerous synapses and/or nonsynaptic boutons. They are certainly accessible to drugs taken by the patients with agonist/

antagonist activity on these receptors. It is well established, for example, that the uptake of NE by noradrenergic varicosities is largely mediated by high-affinity NETs (cf. Trendelenburg, 1991). The monoamine transporters are the therapeutic targets for tricyclic antidepressants, psychostimulants (amphetamine), and cocaine. Serotonin uptake blockers, such as fluoxetine (Prozac), have been used for the treatment of depression, obsessive-compulsive disorder, and sleep and eating disorders.

It has been observed that the activity of GABA transporter is reduced in human epileptic hippocampus (During et al., 1995). Therefore, it was suggested that GABA uptake blockers may be used as anticonvulsive drugs. Although a loss of benzodiazepine binding sites is characteristic of temporal lobe epilepsy, recent data show that an up-regulation of $GABA_A$ receptors (Nusser et al., 1998) in hippocampal dentate gyrus granule cells represents a compensatory mechanism (cf. Fritschy et al., 1999). There is an interaction between serotonergic and GABAergic neurons in the hippocampus (cf. Gulyás et al., 1999); the evoked $GABA_B$ receptor-mediated slow inhibitory postsynaptic potentials (IPSPs) measured in pyramidal cells and mediated via nonsynaptic 5-HT$_{1A}$ receptors (Segal, 1990) are reduced, and the $GABA_A$ receptor-mediated IPSPs are increased (via 5-HT$_3$ and 5-HT$_2$ receptors; Shen and Andrade, 1998), thereby shifting the GABAergic inhibition into the perisomatic region. The possible involvement of GABAergic interneurons (cf. Freund and Buzsáki, 1996) in schizophrenia and other psychoses has been recently reviewed (Keverne, 1999). Inhibitory GABAergic interneurons with their serotonergic, dopaminergic, and cholinergic inputs play an important role in maintaining network oscillations (Buzsáki and Chrobak, 1995).

Cocaine inhibits monoamine (NE, DA, and 5-HT) transporters (Ritz et al., 1987; cf. Lester et al., 1994). As far as its reinforcing action is concerned, the inhibition of the DAT is the most important (Ritz et al., 1987). Cocaine blockade of DAT results in an increased level of extracellular DA (Rocha et al., 1998) in the limbic system, an effect widely accepted to be the primary cause of the reinforcing and additive effects of cocaine (Kuhar et al., 1991).

It seems likely that the mode of effect of 3,4-methylenedioxymethamphetamine (Ecstasy) is mediated via serotonin transporter, producing a heterologous exchange (Rudnick and Wall, 1992). Amphetamine is taken up by NETs and DATs in expense of transporting NE and DA out from the cytoplasm.

It seems plausible that the effects on the manic-depressive state that are due to influences on noradrenergic transmission may be mediated through changes in the release of other transmitters at the cortical level. Several reports have suggested that long- but not short-term treatment with certain tricyclic antidepressants decreases the functional sensitivity of α_2-adrenoceptors

in brain (McMillen et al., 1980; Spyraki and Fibiger, 1980). It has been shown that clonidine inhibition of the acoustic startle reflex in the rat, a behavioral measure of α_2-adrenoceptor sensitivity after desipramine administration, was also attenuated (McMillen et al., 1980; Davis and Menkes, 1982). The presynaptic link between the noradrenergic and serotonergic (Feuerstein et al., 1993) axon terminals, NE, reduces the release of 5-HT and could explain how by increasing the biophase concentration of endogenous NE in the vicinity of α_2 heteroreceptors, a selective NE uptake blocker may inhibit or reduce the release of 5-HT. As a consequence, both α_2- and 5-HT receptors are up-regulated. Under this condition, any increase in 5-HT release might induce suicidal behavior. Thus, the density or sensitivity of the presynaptic α_2-autoreceptor expressed on the noradrenergic varicosities and of the heteroreceptor expressed on the serotonergic varicosities could result in inhibition of neuronal release of NE/5-HT and lead to depression. Increased density (Callado et al., 1998) and sensitivity of α_{2A}-adrenoceptors in prefrontal cortex could represent a common feature of the reduced monoaminergic (noradrenergic and/or serotonergic) function postulated in depression (Garcia-Sevilla et al., 1999).

On the basis of the hypothesis that an increased 5-HT release relieves certain symptoms of depression, blockade of the negative feedback modulation of 5-HT release has become an attractive concept for antidepressant drug development (cf. Göthert and Schlicker, 1997), in particular when combined with selective uptake blocker. α_2-Adrenoceptors other than autoreceptors are also down-regulated by chronic inhibition of NE uptake by tricyclic antidepressant treatment (Bill et al., 1989). Although many studies indicate that a down-regulation of central β-adrenoceptor sensitivity accompanies chronic antidepressant administration, the consequences of such treatment on α_2-adrenoceptor function are more equivocal (Charney et al., 1981; Sugrue, 1988). Accordingly, biochemical and functional studies have demonstrated that depressed patients have an increased density and sensitivity of platelet α_2-adrenoceptors (Piletz et al., 1986) and that these receptor abnormalities are confined to the high-affinity state (α_{2H}) of the receptor that preferentially recognizes agonists (Garcia-Sevilla et al., 1981, 1986, 1987). In addition, a correlation between α_2-adrenoceptors and suicide was established (De Permentier et al., 1997). There is some evidence that suggests that mania is related to disturbances in catecholaminergic neurotransmission (Silverstone, 1985). In contrast to depression, mania may be characterized by increased noradrenergic and/or dopaminergic transmission. An increase in noradrenergic metabolism is supported by the higher excretion of urinary 3-methoxy-4-hydroxyphenylglycol in manic compared with depressive episodes and the notable increase in cerebrospinal fluid NE itself. Moreover, there are some indirect pharmacological data suggesting that drugs able to decrease noradrenergic transmission, such as reserpine, might be associated with an increased incidence of depression and therapeutic effects in mania. Conversely, most tricyclic and monoamine oxidase inhibitor antidepressants potentiate the noradrenergic system and may potentiate manic shifts (cf. Mongeau et al., 1997). Moreover, the α-adrenoceptor agonist clonidine, which decreases firing of the noradrenergic cells of the locus ceruleus by acting preferentially at presynaptic autoreceptors (Svensson et al., 1975) and reduces the NE release, has antimanic properties. Many antipsychotic drugs inhibit MK-801 (dizocilpine) binding to NMDA receptors with IC_{50} values in the micromolar range (Shim et al., 1999), but their clinical effect may not be mediated via these receptors.

There is increasing interest in developing therapeutic agents that will prevent Glu neurotoxicity, an effect mediated via postsynaptic receptors. Therefore, most of the efforts are involved in a search for Glu receptor antagonists. However, presynaptic receptors able to inhibit Glu release offer another target at which the drug would be able to reduce Glu release. This type of drug would be effective in convulsion and in ischemic insult (cf. Tapia et al., 1999). The NMDA receptor may also be involved in a variety of psychiatric illnesses, including schizophrenia (cf. Shim et al., 1999).

It is generally accepted that the activity of cholinergic innervation of the cerebral cortex plays a crucial role in cortical arousal and attention and is critically involved in memory and learning (Dunnett et al., 1991; Harder et al., 1998). The specific lesions of basal nucleus of Meynert produce cognitive impairment, whereas lesions of the medial septum result in large and permanent impairments of certain types of conditional learning. In addition, the discovery that in Alzheimer's disease there is a very substantial loss of this cholinergic input (Whitehouse et al., 1982; cf. Kása et al., 1997) and its involvement in cognitive deficits observed in patients (Dunnett et al., 1991) just further increased the interest in this topic (Giacobini, 1998). Cholinesterase inhibitors are the current drugs of choice in the treatment of Alzheimer's disease (cf. Giacobini, 1998). A direct correlation was found between the level of acetylcholinesterase inhibition, increase in extracellular concentration of ACh in cortex and hippocampus, and cognitive improvement (cf. Kiss et al., 1999). In addition, it has been shown (Kiss et al., 1999) that cholinesterase inhibition enhanced both ACh (Moor et al., 1995) and NE release in the hippocampus. These findings may help to understand the beneficial effect of cholinesterase inhibition in Alzheimer's disease. Similarly, a selective M2 subtype antagonist with an exclusive effect on cholinergic varicosities and able to cross the blood-brain barrier and to increase ACh release by preventing the negative-feedback inhibition of ACh release would be a potential therapy.

Activation of presynaptic inhibitory muscarinic receptors inhibits the excitatory intrinsic fiber synaptic glutamatergic transmission and prevents recall of previously learned memories from interfering with the learning of new memories (Hasselmo and Bower, 1992, 1993; Hasselmo and Schnell, 1994; Hasselmo and Barkai, 1995).

If the cholinergic high-affinity M2 receptor-mediated suppression of intrinsic glutamatergic input to pyramidal cells is in operation, the advantage of increased ACh release can be used in learning, provided the effect of ACh on dendrites to increase excitability of pyramidal cells is not inhibited (cf. Hasselmo and Bower, 1993).

The effect of nicotine to increase NE release (cf. Wonnacott, 1997) and synaptic transmission (cf. Chiodini et al., 1999) from the hippocampal noradrenergic varicosities is in correlation with its beneficial action on learning and memory. Because this effect is mediated via high-affinity nAChRs of presynaptic location (cf. Wonnacott, 1997; cf. Vizi and Kiss, 1998), attempts have been made to find an nAChR agonist for treatment of Alzheimer's patients. It is also a very well established concept that activation of dopaminergic transmission (increase of DA release) via activation of nAChRs is beneficial in Parkinson's disease (cf. Reader and Dewar, 1999).

VII. Summary

The synaptic information flow has been the most frequently studied field of neuroscience for the past ~50 years, but recent developments that point to different types of release of transmitter (Table 1) from varicosities without synaptic contact and receptors and transporters of nonsynaptic location is based on nonsynaptic communication (Vizi and Knoll, 1971; Vizi, 1974, 1979, 1980b, 1984, 1990, 1991; Fuxe and Agnati, 1991; Vizi et al., 1991; Vizi and Lábos, 1991; Bach-y-Rita, 1993; Zoli and Agnati, 1996; Vizi and Kiss, 1998; Zoli et al., 1999) not requiring impulse frequency coding. The findings of Herkenham (1987, 1991) that there are mismatches between release sites and receptors, represented important support for the nonsynaptic interaction hypothesis. The formerly more restricted view of chemical signal transmission within the synapse has to be extended, because considerable evidence has accumulated to show that although the brain is a wired instrument, its neurons, besides cabled information signaling (through synapses), are able to talk to each other without synaptic contact (i.e., "wireless"). These apparently nonsynaptic arrangements furnish an efficient way to influence neuronal activity continuously in a large field, involving vast neuronal ensembles, without directly contacting every single cell. They are comparable with radiowave transmission instead of the telephone system; the message is sent in a long-distance manner, and only a properly tuned receiver can accept it. Thus, only cells that are equipped with proper receptors sensitive to the ligand can accept the chemical message. Because recent studies (Nicholson and Rice, 1991; Routtenberg, 1991) showed that the size of extracellular space is ~20% of brain volume, it is suggested that this is the space in which transmitter released from varicosities can diffuse away from the release site. Because the extracellular concentrations of transmitters in this space are in the nanomolar to micromolar ranges, the receptors of nonsynaptic location are of high affinity. The high-affinity uptake system located nonsynaptically plays a critical role in terminating the effect of transmitters released from nonsynaptic varicosities on receptors expressed nonsynaptically.

The nonsynaptic communication system has a similar degree of selectivity as that of synaptic circuitry but possesses, in addition, a domain of versatility and plasticity in "hardwared" circuitry.

Gone is our understanding of hard-wired neuronal circuitry created for the amplification of digital information in the synapse, with the use of very fast transmitters able to produce "on" and "off" signals within us; we have to change our mentality and accept there is a nonsynaptic communication system that in the brain, an analog information transfer, whose time constant may be seconds or even minutes. The digital information traffic is affected from time to time by chemical messages sent from neurons located far away. Thus, if a transmitter is released from neurons in concert, resulting in a long-lasting high concentration of the transmitter, it will be able to modulate tonically the release of another transmitter.

The original observations made in 1968 and 1969 (Lindmar et al., 1968; Vizi, 1968; Löffelholz and Muscholl, 1969a,b; Paton and Vizi, 1969) that the release of transmitter can be influenced (inhibited or increased) through the activation of presynaptic receptors by chemicals released from another neuron led to a novel mechanism of interaction of neurons equipped with different transmitters and opened a new strategy of drug therapy. Therefore, it seems likely that compounds with a selective effect on high-affinity receptors and transporters expressed on varicosities of nonsynaptic location may represent the beginning of a new generation of innovative drugs.

REFERENCES

Ádám-Vizi V (1992) External Ca^{2+}-independent release of neurotransmitters. *J Neurochem* **58:**395–405.
Alberts P, Bártfai T and Stjärne L (1981) Site(s) and ionic basis of α-autoinhibition and facilitation of ^{3}H-noradrenaline secretion in guinea-pig vas deferens. *J Physiol (Lond)* **312:**297–334.
Alkondon M, Pereira EFR and Albuquerque EX (1996) Mapping the location of functional nicotinic and γ-aminobutyric acid$_A$ receptors on hippocampal neurons. *J Pharmacol Exp Ther* **279:**1491–1506.
Alkondon M, Pereira EFR, Barbosa CTF and Albuquerque EX (1997) Neuronal nicotinic acetylcholine receptor activation modulates γ-aminobutyric acid release

from CA1 neurons or rat hippocampal slices. *J Pharmacol Exp Ther* **283:**1396–1411.

Allen TGJ and Brown DA (1993) M$_2$ muscarinic receptor-mediated inhibition of Ca^{2+} current in rat magnocellular cholinergic basal forebrain neurons. *J Physiol (Lond)* **466:**173–189.

Allen TGJ and Brown DA (1996) Detection and modulation of acetylcholine release from neurites of rat basal forebrain cells in culture. *J Physiol (Lond)* **492:**453–466.

Allgaier C, Agneter E, Feuerstein TJ and Singer EA (1992) Estimation of the biophase concentration of noradrenaline at presynaptic α_2-adrenoceptors in brain slices. *Naunyn-Schmiedeberg's Arch Pharmacol* **345:**402–409.

Allgaier C, Warnke FP, Stangl AP and Feuerstein TJ (1995) Effects of 5-HT receptor agonists on depolarization-induced [^{3}H]-noradrenaline release in rabbit hippocampus and human neocortex. *Br J Pharmacol* **116:**1769–1774.

Amara SG and Kuhar MJ (1993) Neurotransmitter transporters: recent progress. *Annu Rev Neurosci* **16:**73–93.

Andrews N, Zharkovsky A and File SE (1992) Raised [^{3}H]-5HT release and ^{45}Ca^{2+} uptake in diazepam withdrawal: Inhibition by baclofen. *Pharm Biochem Behav* **41:**695–699.

Apparsundaram S, Schroeter S, Giovanetti E and Blakely RD (1998) Acute regulation of norepinephrine transport: II. PKC-modulated surface expression of human norepinephrine transporter proteins. *J Pharmacol Exp Ther* **287:**744–751.

Asztely F, Erdemli G and Kullmann DM (1997) Extrasynaptic glutamate spillover in the hippocampus: Dependence on temperature and the role of active glutamate uptake. *Neuron* **18:**281–293.

Attwell D, Barbour B and Szatkowski M (1993) Nonvesicular release of neurotransmitter. *Neuron* **11:**401–407.

Bach-y-Rita P (1993) Neurotransmission in the brain by diffusion through the extracellular fluid: A review. *Neuroreport* **4:**343–350.

Bagdy E, Solyom S and Harsing LG Jr (1998) Feedback stimulation of somatodendritic serotonin release: A 5-HT$_3$ receptor-mediated effect in the raphe nuclei of the rat. *Brain Res Bull* **45:**203–208.

Baker PF and Crawford AC (1975) A note on the mechanism by which inhibitors of the sodium pump accelerate spontaneous release of transmitter from motor nerve terminals. *J Physiol (Lond)* **247:**209–226.

Balfour DJ (1980) Effects of GABA and diazepam on ^{3}H-serotonin release from hippocampal synaptosomes. *Eur J Pharmacol* **68:**11–16.

Barbour B, Brew H and Attwell D (1988) Electrogenic glutamate uptake in glial cells is activated by intracellular potassium. *Nature (Lond)* **335:**433–435.

Barbour B and Häusser M (1997) Intersynaptic diffusion of neurotransmitter. *Trends Neurosci* **20:**377–384.

Barker EL and Blakely RD (1995) Norepinephrine and serotonin transporters: Molecular targets of antidepressant drugs, in *Psychopharmacology: The Fourth Generation of Progress* (Bloom FE and Kupfer DJ eds) pp 321–333, Raven Press, New York.

Barnard EA, Skolnick P, Olsen RW, Mohler H, Sieghart W, Biggio G, Braestrup C, Bateson AN and Langer SZ (1998) International Union of Pharmacology. XV. Subtypes of γ-aminobutyric acid$_A$ receptors: Classification on the basis of subunit structure and receptor function. *Pharmacol Rev* **50:**291–313.

Barnes JM, Dev KK and Henley JM (1994) Cyclothiazide unmask AMPA-evoked stimulation of [^{3}H]-L-glutamate release from rat hippocampal synaptosomes. *Br J Pharmacol* **113:**339–341.

Baude A, Nusser Z, Molnar E, McIlhinney RA and Somogyi P (1995) High-resolution immunolocalization of AMPA type glutamate receptor subunits at synaptic and nonsynaptic sites in rat hippocampus. *Neuroscience* **69:**1031–1055.

Bean BP (1992) Pharmacology and electrophysiology of ATP-activated ion channels. *Trends Pharmacol Sci* **13:**87–90.

Beaudet A and Descarries L (1978) The monoamine innervation of the cerebral cortex: synaptic and nonsynaptic action terminals. *Neuroscience* **3:**851–860.

Beaudet A and Sotelo C (1981) Synaptic remodeling of serotonin axon terminals in rat agranular cerebellum. *Brain Res* **16:**305–329.

Benveniste H and Hüttemeier PC (1990) Microdialysis: Theory and application. *Prog Neurobiol* **35:**195–215.

Bernáth S (1992) Calcium independent release of amino acid neurotransmitters: Fact or artifact? *Prog Neurobiol* **38:**57–91.

Besret L, Debruyne D, Rioux P, Bonvalot T, Moulin M, Zarifian E and Baron JC (1996) A comprehensive investigation of plasma and brain regional pharmacokinetics of imipramine and its metabolites during and after chronic administration in the rat. *J Pharm Sci* **85:**291–295.

Bettler B and Mulle C (1995) Neurotransmitter receptors. II. AMPA and kainate receptors (Review). *Neuropharmacology* **34:**123–139.

Bickler PE and Hansen BM (1996) α_2-Adrenergic agonists reduce glutamate release and glutamate receptor-mediated calcium changes in hippocampal slices during hypoxia. *Neuropharmacology* **35:**679–687.

Bijak M and Misgeld U (1997) Effects of serotonin through serotonin$_{1A}$ and serotonin$_4$ receptors on inhibition in the guinea-pig dentate gyrus in vitro. *Neuroscience* **78:**1017–1026.

Bill DJ, Hughes IE and Stephens RJ (1989) The effects of acute and chronic desipramine on the thermogenic and hypoactivity responses to α_2-agonists in reserpinized and normal mice. *Br J Pharmacol* **96:**144–152.

Billinton A, Upton N and Bowery NG (1999) GABA$_B$ receptor isoforms GBR1a and GBR1b, appear to be associated with pre- and post-synaptic elements respectively in rat and human cerebellum. *Br J Pharmacol* **126:**1387–1392.

Blakeley AG and Cunnane TC (1979) The packeted release of transmitter from the sympathetic nerves of the guinea-pig vas deferens: an electrophysiological study. *J Physiol (Lond)* **296:**85–96.

Blakeley RD, DeFelice LJ and Hartzell HC (1994) Molecular physiology of norepinephrine and serotonin transporters. *J Exp Biol* **196:**263–281.

Blandizzi C, Dóda M, Tarkovács G, Del Tacca M and Vizi ES (1991) Functional evidence that acetylcholine release from Auerbach plexus of guinea-pig ileum is modulated by α_{2A}-adrenoceptor subtype. *Eur J Pharmacol* **205:**311–313.

Blandizzi C, Tarkovács G, Natale G, Del Tacca M and Vizi ES (1993) Functional

evidence that [^{3}H]acetylcholine and [^{3}H]noradrenaline release from guinea-pig ileal myenteric plexus and noradrenergic terminals is modulated by different presynaptic α_2 adrenoceptor subtypes. *J Pharmacol Exp Ther* **267:**1054–1060.

Boehm S (1999) ATP stimulates sympathetic transmitter release via presynaptic P2X purinoceptors. *J Neurosci* **19:**737–746.

Bonnet J-J, Benmansour S, Costentin J, Parker EM and Cubeddu LX (1990) Thermodynamic analyses of the binding of substrates and uptake inhibitors on the neuronal carrier of dopamine labeled with [^{3}H]GBR 12783 or [^{3}H]mazindol. *J Pharmacol Exp Ther* **253:**1206–1214.

Bowery NG (1993) GABA$_B$ receptor pharmacology. *Annu Rev Pharmacol Toxicol* **33:**109–147.

Bowyer JF and Weiner N (1989) K$^+$ channel and adenylate cyclase involvement in regulation of Ca^{2+}-evoked release of [^{3}H]dopamine from synaptosomes. *J Pharmacol Exp Ther* **248:**514–520.

Bönisch H (1986) The role of co-transported sodium in the effect of indirectly acting sympathomimetic amines. *Naunyn-Schmiedeberg's Arch Pharmacol* **332:**135–141.

Bönisch H and Brüss M (1994) The noradrenaline transporter of the neuronal plasma membrane. *Ann NY Acad Sci* **733:**193–202.

Brickley SG, Cull-Candy SG and Farrant M (1996) Development of a tonic form of synaptic inhibition in rat cerebellar granule cells resulting from persistent activation of GABA$_A$ receptors. *J Physiol (Lond)* **497:**753–759.

Brooks-Kayal AR, Munir M, Jin H and Robinson MB (1998) The glutamate transporter, GLT-1, is expressed in cultured hippocampal neurons. *Neurochem Int* **33:**95–100.

Brown SJ, James S, Reddington M and Richardson PJ (1990) Both A$_1$ and A$_{2A}$ purine receptors regulate striatal acetylcholine release. *J Neurochem* **55:**31–38.

Brundige JM and Dunwiddie TV (1997) Role of adenosine as a modulator of synaptic activity in the central nervous system. *Adv Pharmacol* **39:**353–391.

Budd SL (1998) Mechanisms of neuronal damage in brain hypoxia/ischemia: Focus on the role of mitochondrial calcium accumulation. *Pharmacol Ther* **80:**203–229.

Buma P (1989) Characterization of luteinizing hormone-releasing hormone fibres in the mesencephalic central grey substance of the rat. *Neuroendocrinology* **49:**623–630.

Bunin M and Wightman RM (1998) Quantitative evaluation of 5-hydroxytryptamine (serotonin) neuronal release and uptake: An investigation of extrasynaptic transmission. *J Neurosci* **18:**4854–4860.

Bunin MA, Prioleau C, Mailman RB and Wightman RM (1998) Release and uptake of 5-hydroxytryptamine in the dorsal raphe and substantia nigra reticulata of the rat brain. *J Neurochem* **70:**1072–1087.

Bunin MA and Wightman RM (1999) Paracrine neurotransmission in the CNS: involvement of 5-HT. *Trends Neurosci* **22:**377–382.

Burger PM, Mehl E, Cameron PL, Maycox PR, Baumert M, Lottspeich F, De Camilli P and Jahn R (1989) Synaptic vesicles immunoisolated from rat cerebral cortex contain high levels of glutamate. *Neuron* **3:**715–720.

Buzsáki G and Chrobak JJ (1995) Temporal structure in spatially organized neuronal ensembles: A role for interneuronal networks. *Curr Opin Neurobiol* **5:**504–510.

Bylund DB (1988) α_2 Adrenergic receptors: A historical perspective, in *The α_2 Adrenergic Receptors* (Limbird L ed) pp 1–13, Humana Press, Clifton, NJ.

Bylund DB, Blaxall HS, Murphy TJ and Simmoneaux V (1991) Pharmacological evidence for α_{2C} and α_{2D} adrenergic receptor subtypes, in *Adrenoceptors: Structure, Mechanism, Function* (Szabadi E and Bradshaw CM eds) pp 27–36, Birkhauser Verlag, Basel.

Bylund DB, Blaxall HS, Iversen LJ, Caron MG, Lefkowitz RJ and Lomasney JW (1992) Pharmacological characteristics of α_2-adrenergic receptors: Comparison of pharmacologically defined subtypes with subtypes identified by molecular cloning. *Mol Pharmacol* **42:**1–5.

Bylund DB, Eikenberg DC, Hieble JP, Langer SZ, Lefkowitz RJ, Minneman KP, Molinoff PB, Ruffolo RR Jr and Trendelenburg U (1994) IV International Union of Pharmacology nomenclature of adrenoceptors. *Pharmacol Rev* **46:**121–136.

Bylund DB, Ray-Prenger C and Murphy TJ (1988a) α_{2A} And α_{2B} adrenergic receptor subtypes: Antagonist binding in tissues and cell lines containing only one subtype. *J Pharmacol Exp Ther* **245:**600–607.

Bylund DB, Rudeen PK, Petterborg LJ and Ray-Prenger C (1988b) Identification of α_2-adrenergic receptors in chicken pineal gland using [^{3}H]rauwolscine. *J Neurochem* **51:**81–86.

Callado LF, Meana JJ, Grijalba B, Pazos A, Sastre M and Garcia-Sevilla JA (1998) Selective increase of α_{2A}-adrenoceptor agonist binding sites in brains of depressed suicide victims. *J Neurochem* **70:**1114–1123.

Caulfield MP (1993) Muscarinic receptors: Characterization, coupling and function. *Pharmacol Ther* **58:**319–379.

Caulfield MP and Birdsall NJM (1998) International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. *Pharmacol Rev* **50:**279–290.

Chaki S, Okuyama S, Ogawa S-I and Tomisawa K (1998) Regulation of NMDA-induced [^{3}H]dopamine release from rat hippocampal slices through sigma-1 binding sites. *Neurochem Int* **33:**29–34.

Charney DS, Menkes DB and Heninger GR (1981) Receptor sensitivity and the mechanism of action of antidepressant treatment. *Arch Gen Psychiatry* **38:**1160–1180.

Chen N and Justice JB Jr (1998) Cocaine acts as an apparent competitive inhibitor at the outward-facing conformation of the human norepinephrine transporter: Kinetic analysis of inward and outward transport. *J Neurosci* **18:**10257–10268.

Chiodini FC, Tassonyi E, Hulo S, Bertrand D and Muller D (1999) Modulation of synaptic transmission by nicotine and nicotinic antagonists in hippocampus. *Brain Res Bull* **48:**623–628.

Chittajallu R, Vignes M, Dev KK, Barnes JM, Collingridge GL and Henley JM (1996) Regulation of glutamate release by presynaptic kainate receptors in the hippocampus. *Nature (Lond)* **379:**78–81.

Clarke PBS and Reuben M (1996) Release of [^{3}H]norepinephrine from rat hippocampal synaptosomes by nicotine: Mediaton by different nicotinic receptor subtypes from [^{3}H]dopamine release. *Br J Pharmacol* **117:** 595–606.

Clements JD (1996) Transmitter timecourse in the synaptic cleft: Its role in central synaptic function. *Trends Neurosci* **19:**163–171.

Clements JD, Lester RA, Tong G, Jahr CE and Westbrook GL (1992) The time course of glutamate in the synaptic cleft. *Science (Wash DC)* **258:**1498–1501.

Colquhoun D and Odgen DC (1988) Activation of ion channels in the frog end-plate by high concentrations of acetylcholine. *J Physiol (Lond)* **395:**131–159.

Conn RJ and Pin J-P (1997) Pharmacology and functions of metabotropic glutamate receptors. *Annu Rev Pharmacol Toxicol* **37:**205–237.

Corey JL, Davidson N, Lester HA, Brecha N and Quick MW (1994) Protein kinase C modulates the activity of cloned γ-aminobutyric acid transporter expressed in *Xenopus* oocytes via regulated subcellular redistribution of the transporter. *J Biol Chem* **269:**14759–14767.

Corradetti R, Lo Conte G, Moroni F, Passani MB and Pepeu G (1984) Adenosine decreases aspartate and glutamate release from rat hippocampal slices. *Eur J Pharmacol* **104:**19–26.

Cowen SC and Beart PM (1998) Cyclothiazide and AMPA receptor desensitization: Analyses from studies of AMPA-induced release of [³H]-noradrenaline from hippocampal slices. *Br J Pharmacol* **123:**473–480.

Cunha RA, Constantino MD and Ribeiro JA (1997) Inhibition of [³H]γ-aminobutyric acid release by kainate receptor activation in rat hippocampal synaptosomes. *Eur J Pharmacol* **323:**167–172.

Cunha RA, Johansson B, Fredholm BB, Ribeiro JA and Sebastiao AM (1995) Adenosine A₂A receptors stimulate acetylcholine release from nerve terminals of the rat hippocampus. *Neurosci Lett* **196:**41–44.

Cunha RA, Milusheva E, Vizi ES, Ribeiro JA and Sebastiao AM (1994) Excitatory and inhibitory effects of A₁ and A₂A adenosine receptor activation on the electrically evoked [³H]acetylcholine release from different areas of the rat hippocampus. *J Neurochem* **63:**207–214.

Cutillas B, Espejo M and Ambrosio S (1998) 7-Nitroindazole prevents dopamine depletion caused by low concentrations of MPP⁺ in rat striatal slices. *Neurochem Int* **33:**35–40.

Dale HH (1935) Pharmacology and nerve endings. *Proc R Soc Med Ther Sect* **28:**319–332.

Daszuta A, Chazal G, Garcia S, Oleskevich S and Descarries L (1991) Ultrastructural features of serotonin neurons grafted to adult rat hippocampus: An immunocytochemical analysis of their cell bodies and axon terminals. *Neuroscience* **42:**793–811.

Davis M and Menkes DB (1982) Tricyclic antidepressants vary in decreasing α₂-adrenoceptor sensitivity with chronic treatment: Assessment with clonidine inhibition of acoustic startle. *Br J Pharmacol* **77:**217–222.

Davis GW and Murphey RK (1994) Retrograde signaling and the development of transmitter release properties in the invertebrate nervous system. *J Neurobiol* **25:**740–756.

Dawson TD and Snyder SH (1994) Gases as biological messengers: Nitric oxide and carbon monoxide in the brain. *J Neurosci* **14:**5147–5159.

De Paermentier FD, Mauger JM, Lowther S, Crompton MR, Katona CLE and Horton RW (1997) Brain α₂-adrenoceptors in depressed suicides. *Brain Res* **757:**60–68.

De Potter WP and Chubb IW (1971) The turnover rate of noradrenergic vesicles. *Biochem J* **125:**375–376.

De Potter WP, Chubb IW, Put A and De Schaepdryver AF (1971) Facilitation of the release of noradrenaline and dopamine-β-hydroxylase at low stimulation frequencies by α-blocking agents. *Arch Int Pharmacodyn Ther* **193:**191–197.

Desai MA, Burnett JP and Schoepp DD (1994) Cyclothiazide selectively potentiates AMPA and kainate-induced [³H]norepinephrine release from rat hippocampal slices. *J Neurochem* **63:**231–237.

Desai MA, Valli MJ, Monn JA and Schoepp DD (1995) 1-BCP, a memory-enhancing agent, selectively potentiates AMPA-induced [³H]norepinephrine release in rat hippocampal slices. *Neuropharmacology* **34:**141–147.

Descarries L, Beaudet A and Watkins KC (1975) Serotonin nerve terminals in adult rat neocortex. *Brain Res* **100:**563–588.

Descarries L, Bosler O, Berthelet F and Des Rosiers MH (1980) Dopaminergic nerve endings visualised by high-resolution autoradiography in adult rat neostriatum. *Nature (Lond)* **284:**620–622.

Descarries L, Gisiger V and Steriade M (1997) Diffuse transmission by acetylcholine in the CNS. *Prog Neurobiol* **53:**603–625.

Descarries L, Lemay B, Doucet G and Berger B (1987) Regional and laminar density of the dopamine innervation in adult rat cerebral cortex. *Neuroscience* **21:**807–824.

Descarries L, Séguéla P and Watkins KC (1991) Nonjunctional relationships of monoamine axon terminals in the cerebral cortex of adult rat, in *Volume Transmission in the Brain* (Fuxe K and Agnati LF eds) pp 53–62, Raven Press, New York.

Descarries L, Soucy JP, Lafaille F, Mrini A and Tanguay R (1995) Evaluation of three transporter ligands as quantitative markers of serotonin innervation density in rat brain. *Synapse* **21:**131–139.

Descarries L, Watkins KC and Lapierre Y (1977) Noradrenergic axon terminals in the cerebral cortex of the rat. III. Topometric ultrastructural analyses. *Brain Res* **133:**197–222.

Destexhe A and Sejnowski TJ (1995) G protein activation kinetics and spillover of γ-aminobutyric acid may account for differences between inhibitory responses in the hippocampus and thalamus. *Proc Natl Acad Sci USA* **92:**9515–9519.

Deupree JD, Hinton KA, Cerutis DR and Bylund DB (1996) Buffers differentially alter the binding of [³H]rauwolscine and [³H]RX821002 to the α₂ adrenergic receptor subtypes. *J Pharmacol Exp Ther* **278:**1215–1227.

Dickinson SD, Sabeti J, Larson GA, Giardina K, Rubinstein M, Kelly MA, Grandy DK, Low MJ, Gerhardt GA and Zahniser NR (1998) Dopamine D₂ receptor-deficient mice exhibit decreased dopamine transporter function but no changes in dopamine release in dorsal striatum. *J Neurochem* **72:**148–156.

Dingledine R, Borges K, Bowie D and Traynelis SF (1999) The glutamate receptor ion channels. *Pharmacol Rev* **51:**7–51.

Dingledine R and Korn SJ (1985) γ-Aminobutyric acid uptake and the termination of

inhibitory synaptic potentials in the rat hippocampal slice. *J Physiol (Lond)* **366:**387–409.

Doucet G, Descarries L and Garcia S (1986) Quantification of the dopamine innervation in adult rat neostriatum. *Neuroscience* **19:**427–445.

Dunnett SB, Everitt BJ and Robbins TW (1991) The basal forebrain-cortical cholinergic system: Interpreting the functional consequences of excitotoxic lesions. *Trends Neurosci* **14:**494–500.

During MJ, Ryder KM and Spencer DD (1995) Hippocampal GABA transporter function in temporal-lobe epilepsy. *Nature (Lond)* **376:**174–177.

Ehinger B, Falck B and Sporrong B (1970) Possible axo-axonal synapses between peripheral adrenergic and cholinergic nerve terminals. *Z Zellforsch* **107:**508–521.

Elliott TR (1904) On the action of adrenaline. *J Physiol (Lond)* **31:**20–21.

Elenkov IJ and Vizi ES (1991) Presynaptic modulation of release of noradrenaline from the sympathetic nerve terminals in the rat spleen. *Neuropharmacology* **12:**1319–1324.

Engel G, Göthert M, Hoyer D, Schlicker E and Hillenbrand K (1986) Identity of inhibitory presynaptic 5-hydroxytryptamine (5-HT) autoreceptors in the rat brain cortex with 5-HT₁B binding sites. *Naunyn-Schmiedeberg's Arch Pharmacol* **332:**1–7.

Erecinska M (1997) The neurotransmitter amino acid transport systems: A fresh outlook of an old problem. *Biochem Pharmacol* **36:**3547–3555.

Erulkar SD and Rahamimoff R (1978) The role of calcium ions in tetanic and post-tetanic increase in miniature endplate potential frequency. *J Physiol (Lond)* **278:**501–511.

Farnebo L-O and Hamberger B (1971a) Drug-induced changes in the release of [³H]-noradrenaline from field stimulated rat iris. *Br J Pharmacol* **43:**97–106.

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

Fastbom J and Fredholm BB (1985) Inhibition of [³H]glutamate release from rat hippocampal slices by L-phenylisopropyladenosine. *Acta Physiol Scand* **125:**121–123.

Felder CC (1995) Muscarinic acetylcholine receptors: Signal transduction through multiple effectors. *FASEB J* **9:**619–625.

Feuerstein TJ, Mutschler A, Lupp A, van Nelthoven V, Schlicker E and Göthert M (1993) Endogenous noradrenaline activates α₂-adrenoceptors on serotonergic nerve endings in human and rat neocortex. *J Neurochem* **61:**474–480.

Floor E, Leventhal PS, Wang Y, Meng L and Chen W (1995) Dynamic storage of dopamine in rat brain synaptic vesicles *in vitro*. *J Neurochem* **64:**689–699.

Floran B, Aceves J, Sierra A and Martinez-Fong D (1990) Activation of D₁ dopamine receptors stimulates the release of GABA in the basal ganglia of the rat. *Neurosci Lett* **116:**136–140.

Floran B, Floran L, Sierra A and Aceves J (1997) D₂ receptor-mediated inhibition of GABA release by endogenous dopamine in the rat globus pallidus. *Neurosci Lett* **237:**1–4.

Frank K and Fuortes MGF (1951) Presynaptic and postsynaptic inhibition of non-synaptic reflexes. *Fed Proc* **16:**39–40.

Fredholm BB (1976) Release of adenosine-like material from isolated perfused dog adipose tissue following sympathetic nerve stimulation and its inhibition by adrenergic α-receptor blockade. *Acta Physiol Scand* **96:**422–430.

Fredholm BB and Dunwiddie TV (1988) How does adenosine inhibit transmitter release? *Trends Pharmacol Sci* **9:**130–134.

Freund TF and Buzsáki G (1996) Interneurons of the hippocampus. *Hippocampus* **6:**347–470.

Fritschy J-M, Kiener T, Bouilleret V and Loup F (1999) GABAergic neurons and GABA_A-receptors in temporal lobe epilepsy. *Neurochem Int* **34:**435–445.

Fung SC and Fillenz M (1983) The role of presynaptic GABA and benzodiazepine receptors in the control of noradrenaline release in rat hippocampus. *Neurosci Lett* **42:**61–66.

Fuxe K and Agnati LF (1991) Two principal modes of electrochemical communication in the brain: Volume versus wiring transmission, in *Volume Transmission in the Brain: Novel Mechanisms for Neural Transmission* (Fuxe K and Agnati LF eds) pp 1–10, Raven Press, New York.

Gainetdinov RR, Jones SR, Fumagalli F, Wightman RM and Caron MG (1998) Re-evaluation of the role of the dopamine transporter in dopamine system homeostasis. *Brain Res Rev* **26:**148–153.

Gally JA, Montague PR, Reeke GN Jr and Edelman GM (1990) The NO hypothesis: Possible effects of a short-lived, rapidly diffusible signal in the development and function of the nervous system. *Proc Natl Acad Sci USA* **87:**3547–3551.

Galzin AM, Poirier MF, Lista A, Chodkiewicz JP, Blier P, Ramdine R, Loo H, Roux FX, Redondo A and Langer SZ (1992) Characterization of the 5-hydroxytryptamine receptor modulating the release of 5-[³H]hydroxytryptamine in slices of the human neocortex. *J Neurochem* **59:**1293–1301.

Garcia-Sevilla JA, Escribá PV, Ozaita A, La Harpe R, Walzer C, Eytan A and Guimón J (1999) Up-regulation of immunolabeled α₂A-adrenoceptors, G_i coupling proteins and regulatory receptor kinases in the prefrontal cortex of depressed suicides. *J Neurochem* **72:**282–291.

Garcia-Sevilla JA, Guimon J, Garcia-Vallejo P and Fuister MJ (1986) Biochemical and functional evidence of supersensitive platelet α₂-adrenoceptors in major affective disorder. *Arch Gen Psychiatry* **43:**51–57.

Garcia-Sevilla JA, Udina C, Alvarez E and Casas M (1987) Enhanced binding of clomipramine treatment. *Acta Psychiatr Scand* **75:**150–157.

Garcia-Sevilla JA, Zip AP, Hollingsworth PJ, Greden JF and Smith CB (1981) Platelet α₂-adrenergic receptors in major depressive disorder. *Arch Gen Psychiatry* **38:**1327–1333.

Garthwaite J and Boulton CL (1995) Nitric oxide signalling in the central nervous system. *Annu Rev Physiol* **57:**683–706.

Garthwaite J, Charles SL and Chess-Williams R (1988) Endothelium-derived relaxing factor release on activation of NMDA receptors suggests role as intercellular messenger in the brain. *Nature (Lond)* **336:**385–388.

Geiger JR, Lubke J, Roth A, Frotscher M and Jonas P (1997) Submillisecond AMPA

receptor-mediated signalling at a principal neuron-interneuron synapse. *Neuron* **18:**1009–1023.

Gelagashvili G and Schousboe A (1998) Cellular distribution and kinetic properties of high-affinity glutamate transporters. *Brain Res Bull* **45:**233–238.

Giacobini E (1998) Invited review: Cholinesterase inhibitors for Alzheimer's disease therapy: from tacrine to future applications. *Neurochem Int* **32:**413–419.

Giros B, Jaber M, Jones SR, Wightman RM and Caron MG (1996) Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature (Lond)* **379:**606–612.

Gobbi M, Frittoli E and Mennini T (1990) The modulation of [³H] noradrenaline and [³H]serotonin release from rat brain synaptosomes is not mediated by the α_{2B}-adrenoceptor subtype. *Naunyn-Schmiedeberg's Arch Pharmacol* **342:**382–386.

Gonon FG and Buda MJ (1985) Regulation of dopamine release by impulse flow and by autoreceptors as studied by in vivo voltammetry in the rat striatum. *Neuroscience* **14:**765–774.

Gordon-Weeks PR (1982) Noradrenergic and non-noradrenergic nerves containing small granular vesicles in Auerbach's plexus of the guinea-pig: Evidence against the presence of noradrenergic synapses. *Neuroscience* **7:**2925–2936.

Göthert M and Schlicker E (1991) Regulation of serotonin release in the CNS by presynaptic heteroreceptors, in *Presynaptic Regulation of Neurotransmitter Release* (Feigenbaum J and Hanani M eds) pp 845–876, Springer-Verlag, Berlin/Heidelberg/New York.

Göthert M and Schlicker E (1997) Regulation of 5-HT release in the CNS by presynaptic 5-HT autoreceptors and 5-HT heteroreceptors, in *Serotonergic Neurons and 5-HT Receptors in the CNS* (Baumgarten HG and Göthert M eds) pp 307–350, Springer-Verlag, Berlin/Heidelberg/New York.

Grady SR, Marks MJ and Collins AC (1994) Desensitization of nicotine-stimulated [³H]dopamine release from mouse striatal synaptosomes. *J Neurochem* **62:**1390–1398.

Graefe K-H and Bönisch H (1988) The transport of amines across the axonal membranes of noradrenergic and dopaminergic neurons, in *Handbook of Experimental Pharmacology, Vol 90. Catecholamines I* (Trendelenburg U and Weiner N eds) pp 193–245, Springer-Verlag, Berlin/Heidelberg/New York.

Gray R, Rajan AS, Radcliffe KA, Yakehiro M and Dani JA (1996) Hippocampal synaptic transmission enhanced by low concentrations of nicotine. *Nature (Lond)* **383:**713–716.

Grijalba B, Callado LF, Meana JJ, Garcia-Sevilla JA and Pazos A (1996) α_2-Adrenoceptor subtypes in the human brain: a pharmacological delineation of [³H]RX-821002 binding to membranes and tissue sections. *Eur J Pharmacol* **310:**83–93.

Gu JGG and MacDermott AB (1997) Activation of ATP P2X receptors elicits glutamate release from sensory neuron synapses. *Nature (Lond)* **389:**749–753.

Guimarães S, Figueiredo IV, Caramona MM, Moura D and Paiva MQ (1998) Prejunctional α_{2A}-autoreceptors in the human gastric and ileocolic arteries. *Naunyn-Schmiedeberg's Arch Pharmacol* **358:**207–211.

Gulyás AI, Acsady L and Freund TF (1999) Structural basis of the cholinergic and serotonergic modulation of GABAergic neurons in the hippocampus. *Neurochem Int* **34:**359–372.

Harder JA, Baker HF and Ridley RM (1998) The role of the central cholinergic projections in cognition: Implications of the effect of scopolamine on discrimination learning in monkeys. *Brain Res Bull* **45:**319–326.

Harms HH, Wardeh G and Mulder AH (1978) Adenosine modulates depolarization-induced release of [³H]noradrenaline from slices of rat brain neocortex. *Eur J Pharmacol* **49:**305–308.

Hársing LG Jr and Zigmond MJ (1997) Influence of dopamine on GABA release in striatum: Evidence for D_1-D_2 interactions and nonsynaptic influences. *Neuroscience* **77:**419–429.

Haskó G, Elenkov IJ and Vizi ES (1995) Presynaptic receptors involved in the modulation of release of noradrenaline from the sympathetic nerve terminals of the rat thymus. *Immunol Lett* **47:**133–137.

Hasselmo ME and Barkai E (1995) Cholinergic modulation of activity-dependent synaptic plasticity in the piriform cortex and associative memory function in a network biophysical simulation. *J Neurosci* **15:**6592–6604.

Hasselmo ME and Bower JM (1992) Cholinergic suppression specific to intrinsic not afferent fiber synapses in rat piriform (olfactory) cortex. *J Neurophysiol* **67:**1222–1229.

Hasselmo ME and Bower JM (1993) Acetylcholine and memory. *Trends Neurosci* **16:**218–222.

Hasselmo ME and Schnell E (1994) Laminar selectivity of the cholinergic suppression of synaptic transmission in rat hippocampal region CA1: Computational modeling and brain slice physiology. *J Neurosci* **14:**3898–3914.

Heikkila RE, Orlansky H and Cohen G (1975a) Studies on the distinction between uptake inhibition and release of [³H]dopamine in rat brain tissue slices. *Biochem Pharmacol* **24:**847–852.

Heikkila RE, Orlansky H, Mytilineou C and Cohen G (1975b) Amphetamine: evaluation of d- and l-isomers as releasing agents and uptake inhibitors for [³H]dopamine and [³H]norepinephrine in slices of rat neostriatum and cerebral cortex. *J Pharmacol Exp Ther* **194:**47–56.

Henry JP, Sagne C, Bedet C and Gasnier B (1998) The vesicular monoamine transporter: From chromaffin granule to brain. *Neurochem Int* **32:**227–246.

Herkenham M (1987) Mismatches between neurotransmitter and receptor localization in brain: Observations and implications. *Neuroscience* **23:**1–38.

Herkenham M (1991) Mismatches between neurotransmitter and receptor localization: Implications for endocrine functions in the brain, in *Volume Transmission in the Brain: Novel Mechanisms for Neural Transmission* (Fuxe K and Agnati LF eds) pp 63–87, Raven Press, New York.

Herrero MT, Oset-Gasque MJ, López E, Vicente S and González MP (1999) Mechanism by which GABA, through its GABA_A receptor, modulates glutamate release from rat cortical neurons in culture. *Neurochem Int* **34:**141–148.

Hille B (1992) G protein-coupled mechanisms and nervous signaling. *Neuron* **9:**187–195.

Hoffman BJ, Hansson SR, Mezey E and Palkovits M (1998) Localization and dynamic regulation of biogenic amine transporters in the mammalian central nervous system. *Front Neuroendocrinol* **19:**187–231.

Hoffmann IS and Cubeddu LX (1984) Differential effects of bromocriptine on dopamine and acetylcholine release modulatory receptors. *J Neurochem* **42:**278–282.

Holthoff K and Witte OW (1998) Intrinsic optical signals in vitro: A tool to measure alterations in extracellular space with two-dimensional resolution. *Brain Res Bull* **47:**649–655.

Hoyer D (1990) Serotonin 5-HT₃, 5-HT₄ and 5-HT-M receptors. *Neuropsychopharmacology* **3:**371–383.

Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ, Saxena PR and Humphrey PP (1994) International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev* **46:**157–203.

Hyttel J (1982) Citalopram: Pharmacological profile of a specific serotonin uptake inhibitor with antidepressant activity. *Prog Neuropsychopharmacol Biol Psych* **6:**277–295.

Ikarashi Y, Takahashi A, Ishimaru H, Shiobara T and Maruyama Y (1998) The role of nitric oxide in striatal acetylcholine release induced by N-methyl-D-aspartate. *Neurochem Int* **33:**255–261.

Isaacson JS, Solis JM and Nicoll RA (1993) Local and diffuse synaptic actions of GABA in the hippocampus. *Neuron* **10:**165–175.

Iversen LL and Kelly JS (1975) Uptake and metabolism of γ-aminobutyric acid by neurons and glial cells. *Biochem Pharmacol* **24:**933–938.

Jackisch R, Haaf A, Jeltsch H, Lazarus C, Kelche C and Cassel JC (1999a) Modulation of 5-hydroxytryptamine release in hippocampal slices of rats: Effects of fimbria-fornix lesions on 5-HT_1B-autoreceptor and α_2-heteroreceptor function. *Brain Res Bull* **48:**49–59.

Jackisch R, Stemmelin J, Neufang B, Lauth D, Neughebauer B, Kelche C and Cassel JC (1999b) Sympathetic sprouting: No evidence for muscarinic modulation of noradrenaline release in hippocampal slices of rats with fimbria-fornix lesions. *Exp Brain Res* **124:**17–24.

Jackisch R, Strittmatter H, Kasakov L and Hertting G (1984) Endogenous adenosine as a modulator of hippocampal acetylcholine release. *Naunyn-Schmiedeberg's Arch Pharmacol* **327:**319–325.

Jensen JB, Schousboe A and Pickering DS (1998) AMPA receptor mediated excitotoxicity in neocortical neurons is developmentally regulated and dependent upon receptor desensitization. *Neurochem Int* **32:**505–513.

Kalsner S and Westfall TC (eds) (1990) Presynaptic receptors and the question of autoregulation of neurotransmitter release. *Ann NY Acad Sci* **604:**1–652.

Kamisaki Y, Hamahashi T, Hamada T, Maeda K and Itoh T (1992) Presynaptic inhibition by clonidine of neurotransmitter amino acid release in various brain regions. *Eur J Pharmacol* **217:**57–63.

Kanner BI and Schuldiner BI (1987) Mechanism of transport and storage of neurotransmitters. *CRC Crit Rev Biochem* **22:**1–38.

Kardos J (1999) Recent advances in GABA research. *Neurochem Int* **34:**353–358.

Karkanias GB and Etgen AM (1993) Estradiol attenuates α_2-adrenoceptor-mediated inhibition of hypothalamic norepinephrine release. *J Neurosci* **13:**3448–3455.

Kása P, Hlavati I, Dobo E, Wolff A, Joo F and Wolff JR (1995) Synaptic and non-synaptic cholinergic innervation of the various types of neurons in the main olfactory bulb of adult rat: Immunocytochemistry of choline acetyltransferase. *Neuroscience* **67:**667–677.

Kása P, Rakonczay Z and Gulya K (1997) The cholinergic system in Alzheimer's disease. *Prog Neurobiol* **52:**511–535.

Katz B (1969) The release of neural transmitter substances. Liverpool University Press, Liverpool.

Katz B and Miledi R (1973a) The binding of acetylcholine to receptors and its removal from the synaptic cleft. *J Physiol (Lond)* **231:**549–754.

Katz B and Miledi R (1973b) The effect of atropine on acetylcholine action at the neuromuscular junction. *Proc R Soc Lond B Biol Sci* **184:**221–226.

Katz B and Miledi R (1977) Transmitter leakage from motor nerve endings. *Proc R Soc Lond B Biol* **196:**59–72.

Kauppinenen RA, McMaton HT and Nicholls DG (1988) Ca^{2+}-dependent and Ca^{2+}-independent glutamate release, energy status and cytosolic free Ca^{2+} concentration in isolated nerve terminals following metabolic inhibition: possible relevance to hypoglycaemia and anoxia. *Neuroscience* **27:**175–182.

Kawagoe KT, Garris PA, Wiedemann DJ and Wightman RM (1992) Regulation of transient dopamine concentration gradients in the microenvironment surrounding nerve terminals in the rat striatum. *Neuroscience* **51:**55–64.

Keverne EB (1999) GABAergic neurons and the neurobiology of schizophrenia and other psychoses. *Brain Res Bull* **48:**467–471.

Khakh BS and Henderson G (1998) ATP receptor mediated enhancement of fast excitatory neurotransmitter release in the brain. *Mol Pharmacol* **54:**372–378.

Khakh BS and Kennedy C (1998) Adenosine and ATP: progress in their receptors' structures and functions. *Trends Pharmacol Sci* **19:**39–41.

Kia HK, Brisorgueil M-J, Hamon M, Calas A and Vergé D Ultrastructural localization of 5-hydroxytryptamine_1A receptors in the rat brain. *J Neurosci Res* **46:**697–708.

Kilbinger H, Dietrich C and von Bardeleben RS (1993) Functional relevance of presynaptic muscarinic autoreceptors. *J Physiol* (Paris) **87:**77–81.

Kilpatrick GJ, Bunce KT and Tyers MB (1990) 5-HT₃-receptors. *Med Res Rev* **10:**441–475.

Kirk IP and Richardson PJ (1994) Adenosine A_{2A} receptor-mediated modulation of striatal [³H]GABA and [³H]acetylcholine release. *J Neurochem* **62:**960–966.

Kirpekar SM and Puig M (1971) Effect of flow stop on noradrenaline release from normal spleen and spleens treated with cocaine, phentolamine or phenoxybenzamine. *Br J Pharmacol* **43:**359–369.

Kiss JP, Hennings ECP, Zsilla G and Vizi ES (1999a) A possible role of nitric oxide in the regulation of dopamine transporter function in the striatum. *Neurochem Int* **34:**345–350.

Kiss JP, Sershen H, Lajtha A and Vizi ES (1996) Inhibition of neuronal nitric oxide

synthase potentiates the dimethylphenylpiperazinium-evoked carrier-mediated release of noradrenaline from rat hippocampal slices. *Neurosci Lett* **215:**115–118.

Kiss JP, Vizi ES and Westerink BH (1999b) Effect of neostigmine on the hippocampal noradrenaline release: Role of cholinergic receptors. *Neuroreport* **10:**81–86.

Kiss JP, Zsilla G, Mike A, Zelles T, Toth E, Lajtha A and Vizi ES (1995) Subtype-specificity of the presynaptic α_2-adrenoceptors modulating hippocampal norepinephrine release in rat. *Brain Res* **674:**238–244.

Koch H, von Kügelgen I and Starke K (1997) P2-receptor-mediated inhibition of noradrenaline release in the rat hippocampus. *Naunyn-Schmiedeberg's Arch Pharmacol* **355:**707–715.

Koelle GB (1990) Early evidence of presynaptic receptors. *Ann NY Acad Sci* **604:**488–491.

Kuffler SW and Yoshikami D (1975) The number of transmitter molecules in a quantum: An estimate from iontophoretic application of acetylcholine at the neuromuscular synapse. *J Physiol (Lond)* **251:**465–482.

Kuhar MJ, Ritz MC and Boja JW (1991) The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci* **14:**299–302.

Kulak JM, Nguyen TA, Olivera BM and McIntosh JM (1997) α-Conotoxin MII blocks nicotine-stimulated dopamine release in rat striatal synaptosomes. *J Neurosci* **17:**5263–5270.

Kullmann DM and Asztely F (1998) Extrasynaptic glutamate spillover in the hippocampus: Evidence and implications. *Trends Neurosci* **17:**8–14.

Kullmann DM, Erdemli G and Asztely F (1996) LTP of AMPA and NMDA receptor-mediated signals: Evidence for presynaptic expression and extrasynaptic glutamate spill-over. *Neuron* **17:**461–474.

Kuo M-F, Song D, Murphy S, Papadopoulos MD, Wilson DF and Pastuszko A (1998) Excitatory amino acid receptor antagonists decrease hypoxia induced increase in extracellular dopamine in striatum of newborn piglets. *Neurochem Int* **32:**281–289.

Lacey MG, Mercuri NB and North RA (1987) Dopamine acts on D_2 receptors to increase potassium conductance in neurons of the rat substantia nigra zona compacta. *J Physiol (Lond)* **392:**397–416.

Langer SZ (1974) Presynaptic regulation of catecholamine release. *Biochem Pharmacol* **23:**1793–1800.

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

Langer SZ (1981a) Presynaptic regulation of the release of catecholamines. *Pharmacol Rev* **32:**337–362.

Langer SZ (1981b) Presence and physiological role of presynaptic inhibitory α_2-adrenoceptors in guinea-pig atria. *Nature (Lond)* **294:**671–672.

Langer SZ (1997) 25 Years since the discovery of presynaptic receptors: present knowledge and future perspectives. *Trends Pharmacol Sci* **18:**95–99.

Langer SZ, Scatton B, Schoemaker H and Rein W (1998) Presynaptic autoreceptors and heteroreceptors are both alive and kicking. *Trends Pharmacol Sci* **19:**128–131.

Lapchak PA, Araujo DM, Quirion R and Collier B (1989) Binding sites for [^{3}H]AF-DX 116 and the effect of AF-DX 116 on endogenous acetylcholine release from rat brain slices. *Brain Res* **496:**285–294.

Lawhead RG, Blaxall HS and Bylund DB (1992) α_{2A} is the predominant α_2 adrenergic receptor subtype in human spinal cord. *Anesthesiology* **77:**983–991.

Lena C and Changeux JP (1997) Role of Ca^{2+} ions in nicotinic facilitation of GABA release in mouse thalamus. *J Neurosci* **251:**576–585.

Lena C, Changeux JP and Mulle C (1993) Evidence for 'preterminal' nicotinic receptors of GABAergic axons in the rat interpeduncular nucleus. *J Neurosci* **13:**2680–2688.

Lerma J, Herranz AS, Herreras D, Abraira V and Martin Del Rio R (1986) In vivo determination of extracellular concentration of amino acids in the rat hippocampus. *Brain Res* **384:**145–155.

Lester HA, Cao Y and Mager S (1996) Listening to neurotransmitter transporters. *Neuron* **17:**807–810.

Lester HA, Mager S, Quick MW and Corey JL (1994) Permeation properties of neurotransmitter transporters. *Annu Rev Pharmacol Toxicol* **34:**219–249.

Lester RA and Jahr CE (1990) Quisqualate receptor-mediated depression of calcium currents in hippocampal neurons. *Neuron* **4:**741–749.

Levey AI, Edmunds SM, Koliatsos V, Wiley RG and Heilman CJ (1995) Expression of m1–m4 muscarinic acetylcholine receptor proteins in rat hippocampus and regulation by cholinergic innervation. *J Neurosci* **15:**4077–4092.

Levi G and Raiteri M (1976) Synaptosomal transport processes. *Int Rev Neurobiol* **19:**51–74.

Levi G and Raiteri M (1993) Carrier-mediated release of neurotransmitters. *Trends Neurosci* **16:**415–419.

Liang NY and Rutledge CO (1982) Evidence for carrier-mediated efflux of dopamine from corpus striatum. *Biochem Pharmacol* **31:**2479–2484.

Limberger N, Deicher R and Starke K (1991) Species differences in presynaptic serotonin autoreceptors: Mainly 5-HT$_{1B}$ but possibly in addition 5-HT$_{1D}$ in the rat, 5-HT$_{1D}$ in the rabbit and guinea-pig brain cortex. *Naunyn-Schmiedeberg's Arch Pharmacol* **343:**353–364.

Lindmar R and Löffelholz K (1972) Differential effects of hypothermia on neuronal efflux, release and uptake of noradrenaline. *Naunyn-Schmiedeberg's Arch Pharmacol* **274:**410–414.

Lindmar R, Löffelholz K and Muscholl E (1968) A muscarinic mechanism inhibiting the release of noradrenaline from peripheral adrenergic nerve fibers by nicotinic agents. *Br J Pharmacol* **32:**280–294.

Llinas RR (1977) Depolarization-release coupling systems in neurons. *Neurosci Res Prog Bull* **15:**555–687.

Loewi O (1921) Über humorale Übertragbarkeit der Herznervenwirkung. *Pflügers Arch Gesamte Physiol* **189:**239–242.

Lonart G and Johnson KM (1994) Inhibitory effects of nitric oxide on the uptake of [^{3}H]dopamine and [^{3}H]glutamate by striatal synaptosomes. *J Neurochem* **63:**2108–2117.

Lonart G and Johnson KM (1995a) Characterization of nitric oxide generator-induced hippocampal [^{3}H]norepinephrine release. I. The role of glutamate. *J Pharmacol Exp Ther* **275:**7–13.

Lonart G and Johnson KM (1995b) Characterization of nitric oxide generator-induced hippocampal [^{3}H]norepinephrine release. II. The role of calcium, reverse norepinephrine transport and cyclic $3',5'$-guanosine monophosphate. *J Pharmacol Exp Ther* **275:**14–22.

Loy R, Koziell DA, Lindsey JD and Moore RY (1980) Noradrenergic innervation of the adult rat hippocampal formation. *J Comp Neurol* **189:**699–710.

Löffelholz K and Muscholl E (1969a) A muscarinic inhibition of the noradrenaline release evoked by postganglionic sympathetic nerve stimulation. *Naunyn-Schmiedeberg's Arch Pharmacol* **265:**1–15.

Löffelholz K and Muscholl E (1969b) Inhibitory effect of acetylcholine on the release of noradrenaline from isolated rabbit hearts stimulated sympathetically. *Naunyn-Schmiedeberg's Arch Pharmacol* **263:**236-237.

Lu Y, Grady S, Marks MJ, Picciotto M, Changeux J-P and Collins AC (1998) Pharmacological characterization of nicotinic receptor-stimulated GABA release from mouse brain synaptosomes. *J Pharmacol Exp Ther* **287:**648–657.

MacDermott AB, Role LW and Siegelbaum SA (1999) Presynaptic ionotropic receptors and the control of transmitter release. *Annu Rev Neurosci* **22:**443–485.

MacDonald E, Kobilka BK and Scheinin M (1997) Gene targeting: Homing in on α_2 adrenoceptor-subtype function. *Trends Pharmacol Sci* **18:**211–219.

Majewski H, Costa M, Foucart S, Murphy T and Musgrave IF (1990) Second messengers are involved in facilitatory but not inhibitory receptor actions at sympathetic nerve ending. *Ann NY Acad Sci* **604:**266–275.

Majewski H and Iannazzo L (1998) Protein kinase C: A physiological mediator of enhanced transmitter output. *Prog Neurobiol* **55:**463–475.

Malva JO, Ambrósio AF, Carvalho AP and Carvalho CM (1998b) Increase of the intracellular Ca^{2+} concentration mediated by transport of glutamate into rat hippocampal synaptosomes: Characterization of the activated voltage sensitive Ca^{2+} channels. *Neurochem Int* **32:**7–16.

Malva JO, Carvalho AP and Carvalho CM (1996) Domoic acid induces the release of glutamate in the rat hippocampal CA3 subregion. *Neuroreport* **7:**1330–1334.

Malva JO, Carvalho AP and Carvalho CM (1998a) Kainate receptors in hippocampal CA3 subregion: Evidence for a role in regulating neurotransmitter release. *Neurochem Int* **32:**1–6.

Manber L and Gershon MD (1979) A reciprocal adrenergic-cholinergic axo-axonic synapse in the mammalian gut. *Am J Physiol* **236:**738–745.

Marchi M, Lupinacci M, Bernero E, Bergaglia F and Raiteri M (1999) Nicotinic receptors modulating ACh release in rat cortical synaptosomes: Role of Ca^{2+} ions in their function and desensitization. *Neurochem Int* **34:**319–328.

Marchi M, Paudice P, Bella M and Raiteri M (1986) Dicyclomine and pirenzepine-sensitive muscarinic receptors mediate inhibition of [^{3}H]serotonin release in different rat brain areas. *Eur J Pharmacol* **129:**353–357.

Marchi M and Raiteri M (1989) Interaction acetylcholine-glutamate in rat hippocampus: involvement of two subtypes of M-2 muscarinic receptors. *J Pharmacol Exp Ther* **248:**1255–1260.

Marshal DL, Soliakov L, Redfern P and Wonnacott S (1996) Tetrodotoxin-sensitivity of nicotine-evoked dopamine release from rat striatum. *Neuropharmacology* **35:**1531–1536.

Martin KF, Hannon S, Phillips I and Heal DJ (1992) Opposing roles for 5-HT$_{1B}$ and 5-HT$_3$ receptors in the control of 5-HT release in rat hippocampus in vivo. *Br J Pharmacol* **106:**139–142.

Masland RL and Wigton RS (1940) *J Neurophysiol* **3:**269–275.

Mateo Y, Pineda J and Meana JJ (1998) Somatodendritic α_2-adrenoceptors in the locus coeruleus are involved in the in vivo modulation of cortical noradrenaline release by the antidepressant desipramine. *J Neurochem* **71:**790–798.

Matthews-Bellinger J and Salpeter MM (1978) Distribution of acetylcholine receptors at frog neuromuscular junctions with a discussion of some physiological implications. *J Physiol (Lond)* **279:**197–213.

Maura G and Raiteri M (1986) Cholinergic terminals in rat hippocampus possess 5-HT$_{1B}$ receptors mediating inhibition of acetylcholine release. *Eur J Pharmacol* **129:**333–337.

Maura G, Roccatagliata E and Raiteri M (1986) Serotonin autoreceptor in rat hippocampus: Pharmacological characterization as a subtype of the 5-HT$_1$ receptor. *Naunyn-Schmiedeberg's Arch Pharmacol* **334:**323–326.

Maura G, Thellung S, Andrioli GC, Ruelle A and Raiteri M (1993) Release-regulating serotonin 5-HT$_{1D}$ autoreceptors in human cerebral cortex. *J Neurochem* **60:**1179–1182.

McBain CJ, Traynelis SF and Dingledine R (1990) Regional variation of extracellular space in the hippocampus. *Science (Wash DC)* **249:**674–677.

McGehee DS, Heath MJ, Gelber S, Devay P and Role LW (1995) Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. *Science* **269:**1692–1696.

McGehee DS and Role LW (1996) Presynaptic ionotropic receptors. *Curr Opin Neurobiol* **6:**342–349.

McKinney M, Miller JH and Aagaard PJ (1993) Pharmacological characterization of the rat hippocampal muscarinic autoreceptor. *J Pharmacol Exp Ther* **264:**74–78.

McLean S, Rothman RB, Jacobson AE, Rice KC and Herkenham M (1987) Distribution of opiate receptor subtypes and enkephalin and dynorphin immunoreactivity in the hippocampus of squirrel, guinea pig, rat and hamster. *J Comp Neurol* **255:**497–510.

McMillen BA, Warnack W, German DC and Shore PA (1980) Effects of chronic desipramine treatment on rat brain noradrenergic responses to α-adrenergic drugs. *Eur J Pharmacol* **61:**239–246.

Meiergerd SM, Patterson TA and Schenk JO (1993) D_2 receptors may modulate the function of the striatal transporter for dopamine: Kinetic evidence from studies in vitro and in vivo. *J Neurochem* **61:**764–767.

Miller KJ and Hoffman BJ (1994) Adenosine A3 receptors regulate serotonin transport via nitric oxide and cGMP. *J Biol Chem* **269:**27351–27356.

Milusheva E, Baranyi M, Zelles T, Mike A and Vizi ES (1994) Release of acetylcholine and noradrenaline from the cholinergic and adrenergic afferents in rat hippocampal CA1, CA3 and dentate gyrus regions. *Eur J Neurosci* **6:**187–192.

Milusheva EA, Doda M, Baranyi M and Vizi ES (1996) Effect of hypoxia and glucose

deprivation on ATP level, adenylate energy charge and $[Ca^{2+}]_o$-dependent and independent release of $[^3H]$dopamine in rat striatal slices. *Neurochem Int* **28:**501–507.

Milusheva EA, Doda M, Pasztor E, Lajtha A, Sershen H and Vizi ES (1992) Regulatory interactions among axon terminals affecting the release of different transmitters from rat striatal slices under hypoxic and hypoglycemic conditions. *J Neurochem* **59:**946–952.

Misgeld U, Bijak M and Jarolimek W (1995) A physiological role for GABA$_B$ receptors and the effects of baclofen in the mammalian central nervous system. *Prog Neurobiol* **46:**423–462.

Missale C, Nash SR, Robinson SW, Jaber M and Caron MG (1998) Dopamine receptors: From structure to function. *Physiol Rev* **78:**189–225.

Mitchell JB, Lupica CR and Dunwiddie TV (1993) Activity-dependent release of endogenous adenosine modulates synaptic responses in the rat hippocampus. *J Neurosci* **13:**3439–3447.

Mody I, De Koninck Y, Otis TS and Soltesz I (1994) Bridging the cleft at GABA synapses in the brain. *Trends Neurosci* **17:**517–525.

Moncada S, Higgs A and Furchgott R (1997) XIV. International Union of Pharmacology nomenclature in nitric oxide research. *Pharmacol Rev* **49:**137–142.

Mongeau R, Blier P and de Montigny C (1997) The serotonergic and noradrenergic systems of the hippocampus: Their interactions and the effects of antidepressant treatments. *Brain Res Rev* **23:**145–195.

Montague PR and Gancayco CD, Winn MJ, Marchase RB, Friedlander MJ (1994) Role of NO production in NMDA receptor-mediated neurotransmitter release in cerebral cortex. *Science (Wash DC)* **263:**973–977.

Moor E, DeBoer P, Auth F and Westerink BH (1995) Characterisation of muscarinic autoreceptors in the septo-hippocampal system of the rat: A microdialysis study. *Eur J Pharmacol* **294:**155–161.

Morari M, Marti M, Sbrenna S, Fuxe K, Bianchi C and Beani L (1998) Reciprocal dopamine-glutamate modulation of release in the basal ganglia. *Neurochem Int* **33:**383–397.

Mori A, Shindou T, Ichimura M, Nonaka H and Kase H (1996) The role of adenosine A$_{2a}$ receptors in regulating GABAergic synaptic transmission in striatal medium spiny neurons. *J Neurosci* **16:**605–611.

Morton RA and Davies CH (1997) Regulation of muscarinic acetylcholine receptor-mediated synaptic responses by adenosine receptors in the rat hippocampus. *J Physiol (Lond)* **502:**75–90.

Murphy DL, Wichems C, Li Q and Heils A (1999) Molecular manipulations as tools for enhancing our understanding of 5-HT neurotransmission. *Trends Pharmacol Sci* **20:**246–252.

Muscettola G, Goodwin FK, Potter WZ, Claeys MM and Markey SP (1978) Imipramine and desipramine in plasma and spinal fluid: Relationship to clinical response and serotonin metabolism. *Arch Gen Psychiatry* **35:**621–625.

Muscholl E (1980a) Presynaptic muscarinic control of noradrenaline release, in *Modulation of Neurochemical Transmission* (Vizi ES ed) pp 1–12, Pergamon Press, Oxford/Akadémiai Kiadó, Budapest.

Muscholl E (1980b) Peripheral muscarinic control of norepinephrine release in the cardiovascular system. *Am J Physiol* **239:**713–720.

Nakai T, Milusheva EA, Baranyi M, Uchihashi Y, Satoh T and Vizi ES (1999) Excessive release of $[^3H]$noradrenaline and glutamate in response to simulation of ischemic conditions in rat spinal cord slice preparation: Effect of NMDA and AMPA receptor antagonists. *Eur J Pharmacol* **366:**143–150.

Nelson N (1998) The family of Na^+/Cl^- neurotransmitter transporters. *J Neurochem* **71:**1785–1803.

Nicholls D and Attwell D (1990) The release and uptake of excitatory amino acids. *Trends Pharamcol Sci* **11:**462–468.

Nicholson A and Rice ME (1991) Diffusion of ions and transmitters in the brain cell microenvironment, in *Volume Transmission in the Brain: Novel Mechanisms for Neural Transmission* (Fuxe K and Agnati LF eds) pp 279–294, Raven Press, New York.

Nicholson C (1985) Diffusion from an injected volume of a substance in brain tissue with arbitrary volume fraction and tortuosity. *Brain Res* **333:**325–329.

Nicholson C and Syková E (1998) Extracellular space structure revealed by diffusion analysis. *Trends Neurosci* **21:**207–215.

Nicoll RA and Alger BE (1979) Presynaptic inhibition: Transmitter and ionic mechanism. *Int Rev Neurobiol* **21:**217–258.

Nirenberg MJ, Chan J, Pohorille A, Vaughan RA, Uhl GR, Kuhar MJ and Pickel VM (1997) The dopamine transporter: Comparative ultrastructure of dopaminergic axons in limbic and motor compartments of the nucleus accumbens. *J Neurosci* **17:**6899–6907.

Nirenberg MJ, Vaughan RA, Uhl GR, Kuhar MJ and Pickel VM (1996) The dopamine transporter is localized to dendritic and axonal plasma membranes of nigrostriatal dopaminergic neurons. *J Neurosci* **16:**436–447.

North RA, Slack BE and Suprenant A (1985) Muscarinic M$_1$ and M$_2$ receptors mediate depolarization and presynaptic inhibition in guinea-pig enteric nervous system. *J Physiol (Lond)* **368:**435–452.

Nusser Z (1999) A new approach to estimate the number, density and variability of receptors at central synapses. *Eur J Neurosci* **11:**745–752.

Nusser Z, Hájos N, Somogyi P and Mody I (1998a) Increased number of synaptic GABA$_A$ receptors underlies potentiation at hippocampal inhibitory synapses. *Nature (Lond)* **395:**172–177.

Nusser Z, Sieghart W and Somogyi P (1998b) Segregation of different GABA$_A$ receptors to synaptic and extrasynaptic membranes of cerebellar granule cells. *J Neurosci* **18:**1693–1703.

Ohno K, Okada M, Tsutsumi R, Matsumoto N and Yamaguchi T (1998) Characterization of cyclothiazide-enhanced kainate excitotoxity in rat hippocampal cultures. *Neurochem Int* **32:**265–271.

Oleskevich S, Descarries L and Lacaille JC (1989) Quantified distribution of the noradrenaline innervation in the hippocampus of adult rat. *J Neurosci* **9:**3803–3815.

Oleskevich S, Descarries L, Watkins KC, Seguela P and Daszuta A (1991) Ultra-

structural features of the serotonin innervation in adult rat hippocampus: an immunocytochemical description in single and serial thin sections. *Neuroscience* **42:**777–791.

Onali P, Olianas MC and Gessa GL (1985) Characterization of dopamine receptors mediating inhibition of adenylate cyclase activity in rat striatum. *Mol Pharmacol* **28:**138–145.

Osawa I, Saito N, Koga T and Tanaka C (1994) Phorbol ester-induced inhibition of GABA uptake by synaptosomes and by *Xenopus* oocytes expressing GABA transporter (GAT1). *Neurosci Res* **19:**287–293.

Page G, Chalon S, Barrier L, Piriou A and Huguet F (1998) Characterization of both dopamine uptake systems in rat striatal slices by specific pharmacological tools. *Neurochem Int* **33:**459–466.

Pastor C, Badia A and Sabrià J (1996) Possible involvement of α_1-adrenoceptors in the modulation of $[^3H]$noradrenaline release in rat brain cortical and hippocampal synaptosomes. *Neurosci Lett* **216:**187–190.

Patel DR and Croucher MJ (1997) Evidence for a role of presynaptic AMPA receptors in the control of neuronal glutamate release in the rat forebrain. *Eur J Pharmacol* **332:**143–151.

Pato MT, Murphy DL and DeVane CL (1991) Sustained plasma concentrations of fluoxetine and/or norfluoxetine four and eight weeks after fluoxetine discontinuation. *J Clin Psychopharmacol* **11:**224–225.

Paton WDM and Vizi ES (1969) The inhibitory action of noradrenaline and adrenaline on acetylcholine output by guinea-pig ileum longitudinal muscle strip. *Br J Pharmacol* **35:**10–28.

Pazos A, Cortés R and Palacios JM (1985) Quantitative autoradiographic mapping of serotonin receptors in the rat brain. II. Serotonin-2 receptors. *Brain Res* **346:**231–249.

Pazos A and Palacios JM (1985) Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. *Brain Res* **346:**205–230.

Pende M, Lanza M, Bonanno G and Raiteri M (1993) Release of endogenous glutamic and aspartic acids from cerebrocortex synaptosomes and its modulation through activation of a γ-aminobutyric acidB (GABA$_B$) receptor subtype. *Brain Res* **604:**325–330.

Peters JA, Malone HM and Lambert JJ (1992) Recent advances in the electrophysiological characterization of 5-HT$_3$ receptors. *Trends Pharmacol Sci* **13:**391–397.

Petitet F, Blanchard JC and Doble A (1995) Effects of non-NMDA receptor modulators on $[^3H]$dopamine release from rat mesencephalic cells in primary culture. *J Neurochem* **64:**1410–1412.

Piguet P and Galvan M (1994) Transient and long-lasting actions of 5-HT on rat dentate gyrus neurons in vitro. *J Physiol (Lond)* **481:**629–639.

Piletz JE, Schubert DSP and Halaris A (1986) Evaluation of studies on platelet α_2-adrenoceptors in depressive illness. *Life Sci* **39:**1589–1616.

Pin JP and Bockaert J (1989) Two distinct mechanisms, differentially affected by excitatory amino acids, trigger GABA release from fetal mouse striatal neurons in primary culture. *J Neurosci* **9:**648–656.

Pittaluga A, Asaro D, Pellegrini G and Raiteri M (1987) Studies on $[^3H]$GABA and endogenous GABA release in rat cerebral cortex suggest the presence of autoreceptors of the GABA$_B$ type. *Eur J Pharmacol* **144:**45–52.

Pittaluga A, Bonfanti A and Raiteri M (1997) Differential desensitization of ionotropic non-NMDA receptors having distinct neuronal location and function. *Naunyn-Schmiedeberg's Arch Pharmacol* **356:**29–38.

Pittaluga A, Pattarini R, Severi P and Raiteri M (1996) Human brain N-methyl-D-aspartate receptors regulating noradrenaline release are positively modulated by HIV-1 coat protein gp120. *AIDS* **10:**463–468.

Pittaluga A and Raiteri M (1992a) N-Methyl-D-aspartic acid (NMDA) and non-NMDA receptors regulating hippocampal norepinephrine release. III. Changes in the NMDA receptor complex induced by their functional cooperation. *J Pharmacol Exp Ther* **263:**327–333.

Pittaluga A and Raiteri M (1990b) Release-enhancing glycine-dependent presynaptic NMDA receptors exist on noradrenergic terminals of hippocampus. *Eur J Pharmacol* **191:**231–234.

Pogun S, Baumann MH and Kuhar MJ (1994a) Nitric oxide inhibits $[^3H]$dopamine uptake. *Brain Res* **641:**83–91.

Pogun S, Dawson V and Kuhar MJ (1994b) Nitric oxide inhibits $[^3H]$glutamate transport in synaptosomes. *Synapse* **18:**21–26.

Poncer JC, Shinozaki H and Miles R (1995) Dual modulation of synaptic inhibition by distinct metabotropic glutamate receptors in the rat hippocampus. *J Physiol (Lond)* **485:**121–134.

Popoli P, Betto P, Reggio R and Ricciarello G (1995) Adenosine A$_{2A}$ receptor stimulation enhances striatal extracellular glutamate levels in rats. *Eur J Pharmacol* **287:**215–217.

Privat A, Mansour H and Geffard M (1988) Transplantation of fetal serotonin neurons into the transected spinal cord of adult rats: Morphological development and functional influence. *Prog Brain Res* **78:**155–166.

Qian Y, Galli A, Ramamoorthy S, Risso S, DeFelice LJ and Blakely RD (1997) Protein kinase C regulates human serotonin transporters via altered surface expression in stably transfected HEK-293 cells. *J Neurosci* **17:**45–57.

Quirion R, Wilson A, Rowe W, Aubert I, Richard J, Doods H, Parent A, White N and Meaney MJ (1995) Facilitation of acetylcholine release and cognitive performance by an M$_2$-muscarinic receptor antagonist in aged memory-impaired rats. *J Neurosci* **15:**1455–1462.

Raiteri M, Bonanno G, Maura G, Pende M, Andrioli GC and Ruelle A (1992) Subclassification of release-regulating α_2-autoreceptors in human brain cortex. *Br J Pharmacol* **107:**1146–1151.

Raiteri M, Marchi M and Paudice P (1990c) Presynaptic muscarinic receptors in the central nervous system. *Ann N Y Acad Sci* **604:**113–129.

Raiteri M, Marchi M, Paudice P and Pittaluga A (1990a) Muscarinic receptors mediating inhibition of γ-aminobutyric acid release in rat corpus striatum and their pharmacological characterization. *J Pharmacol Exp Ther* **254:**496–501.

Raiteri M, Maura G, Folghera S, Cavazzani P, Andrioli GC, Schlicker E, Schalnus R and Göthert M (1990b) Modulation of 5-hydroxytryptamine release by presynaptic

inhibitory α_2-adrenoceptors in the human cerebral cortex. *Naunyn-Schmiedeberg's Arch Pharmacol* **342:**508–512.

Ralevic V and Burnstock G (1998) Receptors for purines and pyrimidines. *Pharmacol Rev* **50:**413–492.

Ramamoorthy S, Giovanetti E, Quian Y and Blakely RD (1998) Phosphorylation and regulation of antidepressant-sensitive serotonin transporters. *J Biol Chem* **273:**2458–2466.

Ramon-y-Cajal S (1893) Sur les ganglions et plexus de l'intestin. *C R Soc Biol (Paris)* **5:**217–223.

Reader TA and Dewar KM (1999) Effects of denervation and hyperinnervation on dopamine and serotonin systems in the rat neostriatum implications for human Parkinson's disease. *Neurochem Int* **34:**1–22.

Richards MH (1990) Rat hippocampal muscarinic autoreceptors are similar to the M_2 (cardiac) subtype: Comparison with hippocampal M_1, atrial M_2 and ileal M_3 receptors. *Br J Pharmacol* **99:**753–761.

Richfield EK, Penney JB and Young AB (1989) Anatomical and affinity state comparisons between dopamine D_1 and D_2 receptors in the rat central nervous system. *Neuroscience* **30:**767–777.

Ridet JL, Rajaofetra N, Teilhac JR, Geffard M and Privat A (1993) Evidence for nonsynaptic serotonergic and noradrenergic innervation of the rat dorsal horn and possible involvement of neuron-glia interactions. *Neuroscience* **52:**143–157.

Ritz MC, Lamb RJ, Goldberg SR and Kuhar MJ (1987) Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science (Wash DC)* **237:**1219–1223.

Rocha BA, Fumagalli F, Gainetdinov RR, Jones SR, Ator R, Giros B, Miller GW and Caron MG (1998) Cocaine self-administration in dopamine-transporter knockout mice. *Nat Neurosci* **1:**132–137.

Rogers M, Colquhoun LM, Patrick JW and Dani JA (1997) Calcium flux through predominantly independent purinergic ATP and nicotinic receptors. *J Neurophysiol* **77:**1407–1417.

Ross SB (1991) Synaptic concentration of dopamine in the mouse striatum in relationship to the kinetic properties of the dopamine receptors and uptake mechanism. *J Neurochem* **56:**22–29.

Rothman RB, Herkenham M, Pert CB, Liang T and Cascieri MA (1984) Visualization of rat brain receptors for the neuropeptide, substance P. *Brain Res* **309:** 47–54.

Routtenberg A (1991) Action at a distance: the extracellular spread of chemicals in the nervous system, in *Volume Transmission in the Brain* (Fuxe K and Agnati LF eds) pp 295–298, Raven Press, New York.

Rudnick G and Wall SC (1992) The molecular mechanism of ecstasy [3.4-ethylene-dioxy-methamphetamine (MDMA)] 190 serotonin transporters are targets for MDMA-induced serotonin release. *Proc Natl Acad Sci USA* **89:**1817–1821.

Rusakov DA, Kullman DM and Stewart MG (1999) Hippocampal synapses: Do they talk to their neighbours? *Trends Neurosci* **22:**382–388.

Sandor NT, Brassai A, Puskas A and Lendvai B (1995) Role of nitric oxide in modulating neurotransmitter release from rat striatum. *Brain Res Bull* **36:**483–486.

Sarantis M, Everett K and Attwell D (1988) A presynaptic action of glutamate at the cone output synapse. *Nature (Lond)* **332:**451–453.

Sastre M and Garcia-Sevilla JA (1994a) Density of α_{2A} adrenoceptors and Gi proteins in the human brain: Ratio of high-affinity agonist sites to antagonist sites and effect of age. *J Pharmacol Exp Ther* **269:**1062–1072.

Sastre M and Garcia-Sevilla JA (1994b) α_2-Adrenoceptor subtypes identified by [³H]RX821002 binding in the human brain: The agonist guanoxabenz does not discriminate different forms of the predominant α_{2A}-subtype. *J Neurochem* **63:**1077–1085.

Sato K, Windisch K, Matko I and Vizi ES (1999) Effects of non-depolarizing neuromuscular blocking agents on norepinephrine release from human atrial tissue obtained during cardiac surgery. *Br J Anaesth* **82:**904–909.

Scanziani M, Salin PA, Vogt KE, Malenka RC and Nicoll RA (1997) Use-dependent increases in glutamate concentration activate presynaptic metabotropic glutamate receptors. *Nature (Lond)* **385:**630–634.

Schmitt FO (1984) Molecular regulators of brain function: A new view. *Neuroscience* **13:**991–1001.

Schneider JS, Rothblat DS and DiStefano L (1994) Volume transmission of dopamine over large distances may contribute to recovery from experimental parkinsonism. *Brain Res* **643:**86–91.

Schoffelmeer ANM and Mulder AH (1983) [³H]Noradrenaline release from brain slices induced by an increase in the intracellular sodium concentration: Role of intracellular calcium stores. *J Neurochem* **40:**615–621.

Schoffelmeer ANM, Wierenga EA and Mulder AH (1986) Role of adenylyl cyclase in presynaptic α_2-adrenoceptor and μ-opioid receptor mediated inhibition of [³H]-noradrenaline release from rat brain cortex slices. *J Neurochem* **46:**1711–1717.

Schousboe A (1999) Pharmacologic and therapeutic aspects of the developmentally regulated expression of $GABA_A$ and $GABA_B$ receptors: Cerebellar granule cells as a model system. *Neurochem Int* **34:**373–377.

Schloss P and Williams DC (1998) The serotonin transporter: A primary target for antidepressant drugs. *J Psychopharmacol* **12:**115–121.

Schulz JB, Matthews R, Jenkins BG, Ferrante RJ, Siwek D, Henshaw DR, Cipollini PB, Mecocci P, Kowall NW, Rosen BR and Beal MF (1995) Blockade of neuronal nitric oxide synthase protects against excitotoxicity in vivo. *J Neurosci* **15:**8419–8429.

Schuman EM and Madison DV (1994) Nitric oxide and synaptic function. *Annu Rev Neurosci* **17:**153–183.

Schwartz EA (1987) Depolarization without calcium can release γ-aminobutyric acid from a retinal neuron. *Science (Wash DC)* **238:**350–355.

Schwartz EA and Tachibana M (1990) Electrophysiology of glutamate and sodium co-transport in a glial cell of the salamander retina. *J Physiol (Lond)* **426:**43–80.

Seabrook GR, Easter A, Dawson GR and Bowery BJ (1997) Modulation of long-term potentiation in CA1 region of mouse hippocampal brain slices by $GABA_A$ receptor benzodiazepine site ligands. *Neuropharmacology* **36:**823–830.

Sebastiao AM and Ribeiro JA (1992) Evidence for the presence of excitatory A_2 adenosine receptors in the rat hippocampus. *Neurosci Lett* **138:**41–44.

Segal M (1990) Serotonin attenuates a slow inhibitory postsynaptic potential in rat hippocampal neurons. *Neuroscience* **36:**631–641.

Segovia G and Mora F (1998) Role of nitric oxide in modulating the release of dopamine, glutamate, and GABA in striatum of the freely moving rat. *Brain Res Bull* **45:**275–279.

Seguela P, Watkins KC and Descarries L (1989) Ultrastructural relationships of serotonin axon terminals in the cerebral cortex of the adult rat. *J Comp Neurol* **289:**129–142.

Seguela P, Watkins KC, Geffard M and Descarries L (1990) Noradrenaline axon terminals in adult rat neocortex: An immunocytochemical analysis in serial thin sections. *Neuroscience* **35:**249–264.

Sershen H, Balla A, Lajtha A and Vizi ES (1997) Characterization of nicotinic receptors involved in the release of noradrenaline from the hippocampus. *Neuroscience* **77:**121–130.

Sherrington C (1906) *The Integrative Action of the Nervous System.* Scribner Press, New York.

Shen RY and Andrade R (1998) 5-Hydroxytryptamine₂ receptor facilitates GABAergic neurotransmission in rat hippocampus. *J Pharmacol Exp Ther* **285:**805–812.

Shim SS, Grant ER, Singh S, Gallagher MJ and Lynch DR (1999) Actions of butyrophenones and other antipsychotic agents at NMDA receptors: Relationship with clinical effects and structural considerations. *Neurochem Int* **34:**167–175.

Shinomura T, Nakao S, Adachi T and Shingu K (1999) Clonidine inhibits and phorbol acetate activates glutamate release from rat spinal synaptoneurosomes. *Anesth Analg* **88:**1401–1405.

Sieghart W, Fuchs K, Tretter V, Ebert V, Jechlinger M, Höger H and Adamiker D (1999) Structure and subunit composition of $GABA_A$ receptors. *Neurochem Int* **34:**379–385.

Silverstone T (1985) Dopamine in manic depressive illness: A pharmacological synthesis. *J Affect Disord* **8:**225–231.

Sitte HH, Huck S, Reither H, Boehm S, Singer EA and Pifl C (1998) Carrier-mediated release, transport rates, and charge transfer induced by amphetamine, tyramine, and dopamine in mammalian cells transfected with the human dopamine transporter. *J Neurochem* **71:**1289–1297.

Smiley JF, Levey AI, Ciliax BJ and Goldman-Rakic PS (1994) D_1 dopamine receptor immunoreactivity in human and monkey cerebral cortex: Predominant and extrasynaptic localization in dendritic spines. *Proc Natl Acad Sci USA* **91:**5720–5724.

Somogyi P, Takagi H, Richards JG and Möhler H (1989) Subcellular localization of benzodiazepine/$GABA_A$ receptors in the cerebellum of rat, cat, and monkey using monoclonal antibodies. *J Neurosci* **9:**2197–2209.

Sonders MS, Zhu SJ, Zahniser NR, Kavanaugh MP and Amara SG (1997) Multiple ionic conductances of the human dopamine transporter: The actions of dopamine and psychostimulants. *J Neurosci* **17:**960–974.

Sora I, Wichems C, Takahashi N, Li XF, Zeng Z, Revay R, Lesch KP, Murphy DL and Uhl GR (1998) Cocaine reward models: conditioned place preference can be established in dopamine- and in serotonin-transporter knockout mice. *Proc Natl Acad Sci USA* **95:**7699–7704.

Sperlágh B, Andras I and Vizi S (1997a) Effect of subtype-specific Ca(2+)-antagonists and Ca²⁺-free media on the field stimulation-evoked release of ATP and [³H]acetylcholine from rat habenula slices. *Neurochem Res* **22:**967–975.

Sperlágh B, Sershen H, Lajtha A and Vizi ES (1998) Co-release of endogenous ATP and [³H]noradrenaline from rat hypothalamic slices: Origin and modulation by α_2-adrenoceptors. *Neuroscience* **82:**511–520.

Sperlágh B and Vizi ES (1991) Effect of presynaptic P2 receptor stimulation on transmitter release. *J Neurochem* **56:**1466–1470.

Sperlágh B and Vizi ES (1996) Neuronal synthesis, storage and release of ATP. *Semin Neurosci* **8:**175–186.

Sperlágh B, Zsilla G, Baranyi M, Kékes-Szabó A and Vizi ES (1997b) Age-dependent changes of presynaptic neuromodulation via A_1-adenosine receptors in rat hippocampal slices. *Int J Dev Neurosci* **15:**739–747.

Spyraki C and Fibiger HC (1980) Functional evidence for subsensitivity of noradrenergic α_2-receptors after chronic desipramine treatment. *Life Sci* **27:**1863–1867.

Stamford JA, Kruk ZL and Millar J (1986) *In vivo* voltammetric characterization of low affinity striatal dopamine uptake: Drug inhibition profile and relation to dopaminergic innervation density. *Brain Res* **373:**85–91.

Starke K (1971) Influence of α-receptor stimulants on noradrenaline release. *Naturwissenschaften* **58:**420.

Starke K (1977) Regulation of noradrenaline release by presynaptic receptor systems. *Rev Physiol Biochem Pharmacol* **77:**1–124.

Starke K (1981) Presynaptic receptors. *Annu Rev Pharmacol Toxicol* **21:**7–30.

Starke K, Göthert M and Kilbinger H (1989) Modulation of neurotransmitter release by presynaptic autoreceptors. *Physiol Rev* **69:**864–989.

Starke K, Taube HD and Borowski E (1977) Pre- and postsynaptic receptors in catecholaminergic transmission. *Naunyn-Schmiedeberg's Arch Pharmacol* **297:** 43–44.

Stjärne L (1981) Ionic mechanisms of α-autoinhibition of [³H]noradrenaline secretion in guinea-pig vas deferens: Possible role of extracellular sodium. *Neuroscience* **6:**2759–2771.

Stjärne L (1989) Basic mechanisms and local modulation of nerve impulse-induced secretion of neurotransmitters from individual sympathetic nerve varicosities. *Rev Physiol Biochem Pharmacol* **112:**1–137.

Stuart GJ and Redman SJ (1992) The role of $GABA_B$ receptors in presynaptic inhibition of 1a EPSPs in cat spinal motoneurons. *J Physiol (Lond)* **447:**675–692.

Sugrue MF (1988) A study of the sensitivity of rat brain α_2-adrenoceptors during chronic antidepressants. *Naunyn-Schmiedeberg's Arch Pharmacol* **320:**90–92.

Sun XP and Stanley EF (1996) An ATP-activated, ligand-gated ion channel on a cholinergic presynaptic nerve terminal. *Proc Natl Acad Sci USA* **93:**1859–1863.

Svensson TH, Bunney BS and Aghajanian GK (1975) Inhibition of both noradrenergic and serotonergic neurons in brain by the α-adrenergic agonist clonidine. *Brain Res* **92:**291.

Svoboda J and Sykova E (1991) Extracellular space volume changes in the rat spinal cord produced by nerve stimulation and peripheral injury. *Brain Res* **560:**216–224.

Szabó C (1996) Physiological and pathophysiological roles of nitric oxide in the central nervous system. *Brain Res Bull* **41:**131–141.

Szatkowski M, Barbour B and Attwell D (1990) Non-vesicular release of glutamate from glial cells by reversed electrogenic glutamate uptake. *Nature (Lond)* **348:**443–445.

Taber MT and Fibiger HC (1994) Cortical regulation of acetylcholine release in rat striatum. *Brain Res* **639:**354–356.

Takahashi T, Forsythe ID, Tsujimoto T, Barnes-Davies M and Onodera K (1996) Presynaptic calcium current modulation by a metabotropic glutamate receptor. *Science (Wash DC)* **274:**594–597.

Tansey EM (1998) Not committing barbarisms: Sherrington and the synapse. *Brain Res Bull* **44:**211–213.

Tapia R, Medina-Ceja L and Pena F (1999) On the relationship between extracellular glutamate, hyperexcitation and neurodegeneration, in vivo. *Neurochem Int* **34:**23–32.

Tarnawa I and Vizi ES (1998) 2,3-Benzodiazepine AMPA antagonists. *Restor Neurol Neurosci* **13:**41–57.

Terrian DM, Conner-Kerr TA, Privette TH and Gannon RL (1991) Domoic acid enhances the K+-evoked release of endogenous glutamate from guinea pig hippocampal mossy fiber synaptosomes. *Brain Res* **551:**303–307.

Thompson SM, Capogna M and Scanziani M (1993) Presynaptic inhibition in the hippocampus. *Trends Neurosci* **16:**222–227.

Thureson-Klein Å (1983) Exocytosis from large and small dense cored vesicles in noradrenergic nerve terminals. *Neuroscience* **10:**245–252.

Thureson-Klein Å (1984) The role of large and small noradrenergic vesicles in exocytosis, in *Catecholamines: Basic and Peripheral Mechanisms* (Usdin E and Liss AR) pp 79–87, New York.

Thureson-Klein Å and Stjärne L (1981) Dense cored vesicles in actively secreting noradrenergic neurons, in *Chemical Neurotransmission 75 Years* (Stjärne L, Hedqvist P, Lagercrantz H and Wennmalm A eds) pp 139–164, Academic Press, London.

Toner CC and Stamford JA (1999) Effects of metabolic alterations on dopamine release in an *in vitro* model of neostriatal ischaemia. *Brain Res Bull* **48:**395–399.

Tong G and Jahr CE (1994) Block of glutamate transporters potentiates postsynaptic excitation. *Neuron* **13:**1195–1203.

Toth E, Vizi ES and Lajtha A (1993) Effect of nicotine on levels of extracellular amino acids in regions of the rat brain *in vivo. Neuropharmacology* **32:**827–832.

Törk I (1990) Anatomy of the serotonergic system. *Ann NY Acad Sci* **600:**9–35.

Trendelenburg U (1991) The TIPS lecture: Functional aspects of the neuronal uptake of noradrenaline. *Trends Pharmacol Sci* **32:**334–337.

Trendelenburg A-U, Limberger N and Starke K (1993) Presynaptic α_2-autoreceptors in brain cortex: α_{2D} in the rat and α_{2A} in the rabbit. *Naunyn-Schmiedeberg's Arch Pharmacol* **348:**35–45.

Trendelenburg A-U, Trendelenburg M, Starke K and Limberger N (1994) Release-inhibiting α_2-adrenoceptors at serotonergic axons in rat and rabbit brain: Evidence for pharmacological identity with α_2-autoreceptors. *Naunyn-Schmiedeberg's Arch Pharmacol* **349:**25–33.

Uchihashi Y, Bencsics A, Umeda E, Nakai T, Sato T and Vizi ES (1998) Na+ channel block prevents the ischemia-induced release of norepinephrine from spinal cord slices. *Eur J Pharmacol* **346:**145–150.

Umbriaco D, Garcia S, Beaulieu C and Descarries L (1995) Relational features of acetylcholine, noradrenaline, serotonin and GABA axon terminals in the stratum radiatum of adult rat hippocampus (CA1). *Hippocampus* **5:**605–620.

Umeda E, Satoh T, Nagashima H, Potter PE, Tarkovács G and Vizi ES (1997) $\alpha2A$ subtype of presynaptic $\alpha2$-adrenoceptors modulates the release of [3H]-noradrenaline from rat spinal cord. *Brain Res Bull* **42:**129–132.

Van Horne C, Hoffer BJ, Stromberg I and Gerhardt GA (1992) Clearance and diffusion of locally applied dopamine in normal and 6-hydroxydopamine lesioned rat striatum. *J Pharmacol Exp Ther* **263:**1285–1292.

Van der Kloot W and Molgo J (1994) Quantal acetylcholine release at the vertebrate neuromuscular junction. *Physiol Rev* **74:**899–991.

Vautrin J, Schaffner AE and Barker JL (1994) Fast presynaptic GABAA receptor-mediated Cl− conductance in cultured rat hippocampal neurons. *J Physiol (Lond)* **479:**53–63.

Venkatesan C, Song X-Z, Go C-G, Kurose H and Aoki C (1996) Cellular and subcellular distribution of α_{2A}-adrenergic receptors in the visual cortex of neonatal and adult rats. *J Comp Neurol* **365:**79–95.

Vizi ES (1968) The inhibitory action of noradrenaline and adrenaline on release of acetylcholine from guinea-pig ileum longitudinal strips. *Naunyn-Schmiedeberg's Arch Pharmac Exp Pathol* **259:**199–200.

Vizi ES (1972) Stimulation by inhibition of (Na+, K+, Mg2+) activated ATPase, of acetylcholine release in cortical slices from rat brain. *J Physiol (Lond)* **226:**95–117.

Vizi ES (1974) Interaction between adrenergic and cholinergic systems presynaptic inhibitory effect of noradrenaline on acetylcholine release. *J Neural Transm Suppl* **11:**61–78.

Vizi ES (1978) Na+, K+ activated adenosinetriphosphatase as a trigger in transmitter release. *Neuroscience* **3:**367–384.

Vizi ES (1979) Presynaptic modulation of neurochemical transmission. *Progr Neurobiol* **12:**181–290.

Vizi ES (1980a) Nonsynaptic modulation of transmitter release: Pharmacological implication. *Trends Pharmacol Sci* **1:**172–175.

Vizi ES (1980b) Modulation of cortical release of acetylcholine by noradrenaline released from nerves arising from the rat locus coeruleus. *Neuroscience* **5:**2139–2144.

Vizi ES (1984a) *Nonsynaptic Interactions between Neurons: Modulation of Neurochemical Transmission.* John Wiley and Sons, Chichester/New York.

Vizi ES (1984b) Physiological role of cytoplasmic and non-synaptic release of transmitter. *Neurochem Int* **6:**435–440.

Vizi ES (1990) Synaptic and nonsynaptic cross talk between neurons. *Ann NY Acad Sci* **604:**344–352.

Vizi ES (1991) Nonsynaptic inhibitory signal transmission between axon terminals: Physiological and pharmacological evidence, in *Volume Transmission in the Brain: Novel Mechanisms for Neural Transmission* (Fuxe K and Agnati LF eds) pp 89–96, Raven Press, New York.

Vizi ES (1998) Different temperature dependence of carrier-mediated (cytoplasmic) and stimulus-evoked (exocytotic) release of transmitter: A simple method to separate the two types of release. *Neurochem Int* **33:**359–366.

Vizi ES and Kiss JP (1998) Neurochemistry and pharmacology of the major hippocampal transmitter systems: Synaptic and nonsynaptic interactions. *Hippocampus* **8:**566–607.

Vizi ES, Kiss JP and Elenkov IJ (1991) Presynaptic modulation of cholinergic and noradrenergic neurotransmission: Interaction between them. *News Phys Sci* **6:**119–123.

Vizi ES and Knoll J (1971) The effects of sympathetic nerve stimulation and guanethidine on parasympathetic neuroeffector transmission, the inhibition of acetylcholine release. *J Pharm Pharmacol* **23:**918–925.

Vizi ES and Knoll J (1976) The inhibitory effect of adenosine and related nucleotides on the release of acetylcholine. *Neuroscience* **1:**391–398.

Vizi ES and Lábos E (1991) Nonsynaptic interactions at presynaptic level. *Progr Neurobiol* **37:**145–163.

Vizi ES and Lendvai B (1997) Side effects of nondepolarizing muscle relaxants: Relationship to their antinicotinic and antimuscarinic actions. *Pharmacol Ther* **73:**75–89.

Vizi ES and Lendvai B (1999) Modulatory role of presynaptic nicotinic receptors in synaptic and nonsynaptic chemical communication in the central nervous system. *Brain Res Rev*, in press.

Vizi ES, Mike A and Tarnawa I (1996) 2,3-Benzodiazepines (GYKI 52466 and analogs): Negative allosteric modulators of AMPA receptors. *CNS Drug Rev* **2:**91–126.

Vizi ES, Mike A and Tarnawa I (1997) The functional study of kainate receptors: Hopes and doubts. *Trends Neurosci* **20:**396–397.

Vizi ES, Orsó E, Osipenko ON, Haskó G and Elenkov I (1995a) Neurochemical, electrophysiological and immunocytochemical evidence for a noradrenergic link between the sympathetic nervous system and thymocytes. *Neuroscience* **68:**1263–1276.

Vizi ES, Sershen H, Balla A, Mike A, Windisch K, Juranyi Z and Lajtha A (1995b) Neurochemical evidence of heterogeneity of presynaptic and somatodendritic nicotinic acetylcholine receptors. *Ann NY Acad Sci* **757:**84–99.

Vizi ES, Somogyi GT, Hársing LG Jr and Zimanyi I (1985) External Ca-independent release of norepinephrine by sympathomimetics and its role in *negative feedback* modulation. *Proc Natl Acad Sci USA* **82:**8775–8780.

Vizi ES and Sperlágh B (1999) Separation of carrier-mediated and vesicular release of GABA from rat brain slices. *Neurochem Int* **34:**407–413.

Von Kügelgen I, Späth L and Starke K (1992) Stable adenine nucleotides inhibit [3H]noradrenaline release in rabbit brain cortex slices by direct action at presynaptic adenosine A1-receptors. *Naunyn-Schmiedeberg's Arch Pharmacol* **346:**187–196.

Von Kügelgen I, Späth L and Starke K (1994) Evidence for P2-purinoceptor-mediated inhibition of noradrenaline release in rat brain cortex. *Br J Pharmacol* **113:**815–822.

Wall SJ, Wolfe BB and Kromer LF (1994) Cholinergic deafferentation of dorsal hippocampus by fimbria-fornix lesioning differentially regulates subtypes (m1–m5) of muscarinic receptors. *J Neurochem* **62:**1345–1351.

West AR and Galloway MP (1999) Nitric oxide and potassium chloride-facilitated striatal dopamine efflux *in vivo*: Role of calcium-dependent release mechanisms. *Neurochem Int* **33:**493–501.

West DP and Fillenz M (1980) Storage and release of noradrenaline in hypothalamic synaptosomes. *J Neurochem* **35:**1323–1328.

Westfall TC (1977) Local regulation of adrenergic neurotransmission. *Phys Rev* **57:**659–728.

Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT and DeLong M (1982) Alzheimer's disease and senile dementia: Loss of neurons in the basal forebrain. *Science (Wash DC)* **215:**1237–1239.

Whiting PJ (1999) The GABAA receptor gene family: New targets for therapeutic intervention. *Neurochem Int* **34:**387–390.

Wightman RM, Amatore C, Engstrom RC, Hale PD, Kristensen EW, Kuhr WG and Hale LJ (1988) Real time characterization of dopamine overflow and uptake in the rat striatum. *Neuroscience* **25:**513–523.

Wilkie GI, Hutson P, Sullivan JP and Wonnacott S (1996) Pharmacological characterization of a nicotinic autoreceptor in rat hippocampal synaptosomes. *Neurochem Res* **21:**1141–1148.

Winzer-Sershan UH, Raymon HK, Broide RS, Chen Y and Leslie FM (1997a) Expression of α_2 adrenoceptors during rat brain development. I. α_{2A} messenger RNA expression. *Neuroscience* **76:**241–260.

Winzer-Sershan UH, Raymon HK, Broide RS, Chen Y and Leslie FM (1997b) Expression of α_2 adrenoceptors during rat brain development . II. α_{2C} messenger RNA expression and [3H]rauwolscine binding. *Neuroscience* **76:**261–272.

Wonnacott S (1997) Presynaptic nicotinic ACh receptors. *Trends Neurosci* **20:**92–98.

Wonnacott S, Irons J, Rapier C, Thorne B and Lunt GG (1989) Presynaptic modulation of transmitter release by nicotinic receptors. *Prog Brain Res* **79:**157–163.

Wonnacott S, Wilkie G, Soliakov L and Whiteaker P (1995) Presynaptic nicotinic autoreceptors and heteroreceptors in the CNS, in *Effects of Nicotine on Biological Systems: Advances in Pharmacological Sciences, Vol. II.* (Clarke P, Quik M, Adlkofer F and Thurau K eds) pp 87–94, Birkhauser Verlag Press, Basel.

Wu L-G and Saggau P (1997) Presynaptic inhibition of elicited neurotransmitter release. *Trends Neurol Sci* **20:**204–212.

Yamazaki T, Akiyama T, Kitagawa H, Takauchi Y and Kawada T (1996) Elevation

of either axoplasmic norepinephrine or sodium level induced release of norepinephrine from cardiac sympathetic nerve terminals. *Brain Res* **737:**343–346.

Yung KK, Bolam JP, Smith AD, Hersch SM, Ciliax BJ and Levey AI (1995) Immunocytochemical localization of D_1 and D_2 dopamine receptors in the basal ganglia of the rat: Light and electron microscopy. *Neuroscience* **65:**709–730.

Zahniser NR, Gerhardt GA, Hoffman AF and Lupica CR (1998) Voltage-dependency of the dopamine transporter in rat brain. *Adv Pharmacol* **42:**195–198.

Zazpe A, Artaiz I and Del Rio J (1994) Role of 5-HT$_3$ receptors in basal and K$^+$-evoked dopamine release from rat olfactory tubercle and striatal slices. *Br J Pharmacol* **113:**968–972.

Zevin S, Gourlay SG and Benowitz NL (1998) Clinical pharmacology of nicotine. *Clin Dermatol* **16:**557–564.

Zhang L, Coffey LL and Reith EA (1997) Regulation of functional activity of the human dopamine transporter by protein kinase C. *Biochem Pharmacol* **53**:677–688.

Zhang YX, Yamashita H, Oshita T, Sawamoto N and Nakamura S (1996) ATP induces release of newly synthesized dopamine in rat striatum. *Neuroscience* **28:**395–400.

Zhu PC, Thureson-Klein Å and Klein RL (1986) Exocytosis from large dense cored vesicles outside the active synaptic zones of terminals within the trigeminal subnucleus caudalis: A possible mechanism for neuropeptide release. *Neuroscience* **19:**43–54.

Zhu S-J, Kavanaugh MP, Sonders MS, Amara SG and Zahniser NR (1997) Activation of protein kinase C inhibits uptake, currents and binding associated with the human dopamine transporter expressed in *Xenopus* oocytes. *J Pharmacol Exp Ther* **282:**1358–1365.

Zoli M and Agnati LF (1996) Wiring and volume transmission in the central nervous system: The concept of closed and open synapses. *Prog Neurobiol* **49:**363–380.

Zoli M, Jansson A, Syková E, Agnati LF and Fuxe K (1999) Volume transmission in the CNS and its relevance for neuropsychopharmacology. *Trends Pharmacol Sci* **20:**142–150.