CENTRAL NORADRENERGIC CONTROL OF BLOOD PRESSURE

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A. Scriabine, B. V. Clineschmidt, and C. S. Sweet
Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486

The importance of central catecholaminergic neurons in the control of systemic arterial pressure has been revealed to a great extent through pharmacological studies, for example, investigations on the mechanisms of action of antihypertensive drugs such as methyldopa and clonidine. The use of pharmacological tools like 6-hydroxydopamine has also yielded important information that probably was unattainable by any other means. Our intention is to review pertinent studies that were basically pharmacological in nature, after first briefly considering the distribution of catecholaminergic neurons in the brain and spinal cord.

DISTRIBUTION

The distribution of norepinephrine-containing nerve terminals and cell bodies in the central nervous system (CNS) provides in itself sufficient reason for seriously considering that this monoamine participates in the central integration and regulation of systemic arterial blood pressure. With the Falck-Hillarp histochemical fluorescence method, groups of cell bodies containing norepinephrine were visualized principally in the medulla and pons, the A1, A2, and A4-7 cell groups of Dahlström & Fuxe's classification (1). Axons emanating from these cell bodies, as visualized also by the Falck-Hillarp technique, organize into ascending dorsal and ventral bundles (2) and a descending bulbospinal system. Practically all noradrenergic cell groups in the medulla and pons contribute fibers to the ventral bundle (3), whereas the bulbospinal system receives input only from the two most caudal cell groups, A1 and A2 (4). The organization of the ascending noradrenergic fibers as revealed by the more recent and more sensitive glyoxylic acid fluorescence method (5) indicates a greater degree of complexity than previously described, but the details are beyond the scope of the present review. Of particular importance with regard to the control of arterial pressure is the demonstrated (6) high density of norepinephrine-containing terminals in the nucleus tractus solitarii (NTS), nucleus dorsalis motorius nervi vagi, and sympathetic intermediolateral columns, as well as a varying density of noradrener-

gic terminals throughout the hypothalamus. The terminals close to preganglionic sympathetic neurons in the spinal cord originate from cell bodies situated in the ventrolateral part of the reticular formation (A1 group) and from cell bodies lying in the area of the solitary-vagal complex, including the nucleus commissuralis (A2 group). Thus, the NTS contains noradrenergic cell bodies and receives a noradrenergic input. The origin of the noradrenergic neurons terminating in the NTS remains somewhat vague but their possible significance is clear since one of the primary relay points for baroreceptor afferents is in the NTS (7). The hypothalamus, which exerts well-known and important influences on baroreceptor reflexes and sympathetic nervous outflow, receives its highly complex noradrenergic input from the ascending noradrenergic fiber systems (2, 5).

Recently the possibility has arisen that epinephrine, in addition to norepinephrine, could also be involved in the central control of arterial pressure. Epinephrine in mammalian brain accounts for approximately only 10% of the total amount of norepinephrine and epinephrine. However, results from recent studies support the proposal of an independent neuronal network containing epinephrine in the rat brain. The distribution of these putative adrenergic neurons has been explored indirectly by the immunocytochemical localization in neurons of phenylethanolamine-N-methyltransferase (PNMT) (8–10), the enzyme that catalyzes conversion of norepinephrine to epinephrine, and with a sensitive radio-enzymatic assay for PNMT (11). The distribution of epinephrine has also been examined more directly in some nuclei and other areas of rat brain using mass fragmentography (12). Based on the immunohistochemical studies of Hökfelt and co-workers (9, 10), epinephrine-containing cell bodies have so far been located in two cell clusters, termed C1 and C2, and their locations correspond to the A1 and A2 cell groups of Dahlström & Fuxe. Furthermore, the density of adrenergic terminals (specifically PNMT positive terminals) is high in NTS, nucleus dorsalis motorius nervi vagi, and the lateral sympathetic columns, whereas the density of terminals varies in different regions of the hypothalamus. Thus, the putative adrenergic neurons are well placed for exerting control over the cardiovascular system.

NORADRENERGIC NEURONS IN EXPERIMENTAL HYPERTENSION

Two recent extensive reviews covered this topic in detail (13, 14); therefore, only the most pertinent reports are dealt with here. Hypertension in the rat can be produced by bilateral lesions of NTS (15). Noradrenergic neurons are apparently involved, because 6-hydroxydopamine administered intracisternally prevented this form of hypertension (16). 6-Hydroxydopamine administered centrally has also been reported to prevent other forms of hypertension including neurogenic hypertension produced by sinoaortic denervation (17), hypertension in spontaneously hypertensive (SH) rats, DOCA-salt, and renal hypertension (18). Lewis and co-workers (19) reported that depletion of brain catecholamines by intracisternal 6-hydroxydopamine in rabbits significantly attenuated the rise in arterial pressure following wrapping the kidney in cellophane. Because the early phase in arterial

renal hypertension is under the control of the renin-angiotensin system, Lewis's study suggested an interrelationship between the kidney and the central nervous system. Of interest was their observation that the pressor response to intraventricular angiotensin was significantly reduced by 6-hydroxydopamine. Severs & Daniels-Severs (20) have recently reviewed the effects of angiotensin II on the CNS. Currently it is understood that the site of the central hypertensive effects of angiotensin II is the nucleus mesencephalicus in the midbrain and/or the area postrema in the caudal half of the medulla. These sites are heavily innervated by noradrenergic nerves.

CENTRAL CARDIOVASCULAR EFFECTS OF α-ADRENERGIC AGONISTS

Norepinephrine and Related Substances

Norepinephrine elicits a fall in systemic pressure and bradycardia following intracerebroventricular (i.c.v.) administration in the anesthetized dog (21–23), cat (24–26), rat (27), and rabbit (28). Prior i.c.v. injection of phentolamine (22) or phenoxybenzamine (23) markedly diminishes these actions of norepinephrine, suggesting that central receptors similar to the peripheral α-adrenergic receptor are involved. Moreover, other α-adrenergic receptor agonists such as α-methylnorepinephrine (29), dopamine (27), epinephrine (24), and phenylephrine (23) have also been reported to produce hypotension and bradycardia after i.c.v. administration. Using unanesthetized cats, Day & Roach (30) reported hypotensive and cardiac-slowing effects following i.c.v. administration of norepinephrine or α-methylnorepinephrine; both effects were abolished after i.c.v. administration of phentolamine. Similar results were obtained when epinephrine was given i.c.v., but only if the β-adrenergic receptor blocking agent, propranolol, was first injected centrally. Of importance was Baum & Shropshire's (27) finding of reduced electrical activity in lumbar sympathetic chains after i.c.v. injection of norepinephrine or dopamine. These observations suggest that activation of α-adrenergic receptors in the CNS leads to hypotension and bradycardia. The location of these receptors is an important point that has received attention only recently. Struyker Boudier et al (31) surveyed several sites in the rat hypothalamus, extending in a caudal-rostral direction from the mammillary area to the preoptic region, to determine whether arterial pressure and heart rate were reduced upon injection of norepinephrine. Hypotension and bradycardia were consistently elicited from the anterior hypothalamic/preoptic region (AH/PO) and phentolamine applied locally was an effective antagonist. Phenylephrine was more effective than oxymetazoline in reducing blood pressure and heart rate when microinjected into the AH/PO area (32) even though both agents were approximately equal as stimulants of peripheral α-adrenergic receptors. This observation may reflect a subtle difference between typical peripheral α-adrenergic receptors and the central α-adrenergic receptors mediating hypotension and bradycardia. Such an explanation could perhaps account for the finding (33) that epinephrine was about ten times more potent than norepinephrine upon application to the AH/PO region. De Jong (34) microinjected norepinephrine

into the NTS in rats and found a decrease in systemic arterial pressure and heart rate, an effect susceptible to blockade by locally administered phentolamine.

According to Neumayr et al (35), electrical stimulation in cats near the areas of the solitary-vagal complex (i.e. near the A2 cell group) or in the ventrolateral reticular region (i.e. close to the A1 group) produces pressor responses and sympathetic discharge. These investigators proposed that the bulbospinal noradrenergic pathway excites preganglionic sympathetic neurons. This proposal is consistent with an accelerated turnover of norepinephrine in the thoracolumbar cord in rabbits with neurogenic hypertension (36). However, Coote & Macleod (37) reached the opposite conclusion. They suggest that the descending noradrenergic pathway arising from A1 cell cluster is inhibitory to sympathetic outflow. Furthermore, in the rat, electrical stimulation near the NTS region was recently reported to lower arterial pressure and heart rate (38).

Methyldopa

The possible relationship between central α-adrenergic receptors and the mode of action of methyldopa was reviewed recently by Van Zwieten (39) and Day & Roach (40). Upon entering the central nervous system, methyldopa undergoes decarboxylation via L-aromatic amino acid decarboxylase and hydroxylation via dopamine-β-hydroxylase to form α-methyldopamine and α-methylnorepinephrine (41). The dependence of the antihypertensive effect of methyldopa on the formation of these metabolites in the CNS was first clearly demonstrated by Henning & Van Zweiten (42, 43). Inhibition of decarboxylase in peripheral tissues with carbidopa did not substantially alter the hypotensive effect of methyldopa in renal hypertensive rats, whereas inhibition of both peripheral and central decarboxylase with benserazide (RO 4–4602) abolished the response. Evidence has also been obtained indicating that conversion of α-methyldopamine to α-methylnorepinephrine is important for the full expression of the hypotensive effect of methyldopa (44–47). It is well established that the central nervous system is the principal site of action of methyldopa. Furthermore, it is clear that α-methylnorepinephrine is the active metabolite. It has been hypothesized that α-methylnorepinephrine released from monoaminergic neurons interacts with central α-adrenergic receptors more strongly than norepinephrine itself, thus effecting a reduction in blood pressure—a variation of the orlginal "false transmitter" hypothesis (40). α-Methylnorepinephrine and norepinephrine appear to be equiactive with respect to decreasing arterial pressure following i.c.v. administration (30, 47), although the α-methylated compound may have a longer duration of action (30). Injection of α-methylnorepinephrine into the AH/PO region in the rat induced depressor effects at doses lower than those needed to obtain depressor effects with norepinephrine (48). α-Methylnorepinephrine also appears to be more effective than norepinephrine in decreasing blood pressure and heart rate following injection into the NTS of the medulla oblongata (49). The greater efficacy of α-methylnorepinephrine may be the result of less effective inactivation mechanisms for the α-methylated compound or of some difference in the ability of α-methylnorepinephrine and norepinephrine to activate central α-adren-

ergic receptors. Whether α-methylnorepinephrine acts on postjunctional receptors to facilitate synaptic transmission or on prejunctional α-adrenergic receptors (see below) to inhibit noradrenergic or adrenergic transmission remains to be ascertained.

Clonidine

The first clinical observation suggesting a utility for α-adrenergic stimulants in the treatment of hypertension was made in 1957 by Finnerty et al (50). They observed that a nasal decongestant, tetrahydrozoline, an imidazoline with α-adrenergic stimulant properties, given orally lowered arterial pressure in hypertensive patients. The mechanism of antihypertensive action of tetrahydrozoline was not established. Subsequent pharmacological studies characterized this drug as a peripheral α-adrenergic stimulant that lowered cardiac output and heart rate possibly by a central action (51, 52). Numerous related imidazolines had similar activity (53). The importance of α-adrenergic receptors in the control of arterial pressure has been revealed largely by studies on the mode of action of clonidine (54). Van Zwieten reviewed the earlier pharmacological and clinical studies with clonidine emphasizing its central site of action (55).

According to Schmitt et al (56), clonidine decreased the sympathetic activity in the splanchnic and cardiac nerves in normal animals as well as in animals with denervated carotid sinuses. Clonidine had pronounced hypotensive activity when injected or infused into the vertebral artery of cats or dogs (57, 58); it also reduced arterial pressure by intracisternal administration of doses that were ineffective when injected intravenously (59). In cross-circulation experiments, clonidine administered into the arterial inflow of neurally intact but vascularly isolated heads of recipient dogs led to a decrease in arterial pressure in both the recipient and donor dogs (60).

Several studies suggest that the hypotensive and cardiac-slowing effects of clonidine involve α-adrenergic receptors. For example, it has been shown that the hypotensive effect of clonidine in rabbits was reduced by α-adrenergic blocking agents, tolazoline, and phenoxybenzamine (61). Also, an α-adrenergic blocking agent, piperoxane, by either intravenous or intracisternal administration antagonized the hypotensive and cardiac-slowing effects of clonidine in cats (62). These and other studies (63, 64) on the interaction of clonidine with α-adrenergic blocking drugs led to the conclusion that clonidine interacts with α-adrenergic receptors to decrease blood pressure and heart rate.

In addition to reducing sympathetic outflow to the heart, clonidine was also shown to enhance pressure-sensitive compensatory reflexes (65–68). This effect was found to be vagally mediated. Further studies of this phenomenon (69–71) indicated that clonidine acted on the central nervous system to enhance vagal activity and that this action also involved central α-adrenergic receptors.

The site of central hypotensive action of clonidine has been the subject of numerous investigations. Destruction of a medullary depressor area in cats and dogs antagonized the hypotensive effect of clonidine (72). Because the effects of clonidine were, however, never completely abolished, other sites of action of clonidine must

be considered (72). Further studies on localization of the site of central hypotensive action of clonidine in cats led to the conclusion that clonidine exerts its action on "chemosensitive zones" located on the ventral surface of the brain stem (73). There is also evidence that an additional site of action of clonidine may be the spinal cord. In spinal cats, stimulation of the dorsal lateral column below the transection caused sympathetic discharge that was reduced by clonidine (74). Klevans et al (75) have also presented some evidence that supramedullary structures are involved in central cardiovascular effects of clonidine. On the basis of studies discussed above, it can be concluded that clonidine acts at multiple sites within the central nervous system.

Several investigators have considered the possibility that dopaminergic or serotonergic systems might be involved in the mechanism of the hypotensive action of clonidine. The hypotensive effect of clonidine in cats was not blocked by dopaminergic blocking agents, pimozide and spiroperidol (76).

According to other investigators, however, dopamine and clonidine, but not norepinephrine, lowered arterial pressure when applied to the ventral surface of the brain stem in cats. These effects of clonidine and dopamine were blocked by pimozide (77). In DOCA-saline hypertensive rats, the antihypertensive effect of clonidine was not modified by 5, 6-dihydroxytryptamine or *p*-chloro-N-methylamphetamine, drugs that destroy central serotonin-containing neurons, but was antagonized by desipramine, piperoxane, or phentolamine (78).

In addition to previously described effects of clonidine on the central nervous system, the drug also inhibits sympathetic transmission at a peripheral site or sites. Scriabine et al (79, 80) reported that clonidine reduced heart rate in dogs with spinal cord sectioned at the level of the second cervical vertebra, antagonized the pressor and positive chronotropic effects of a muscarinic ganglionic stimulant, McN A-343 (4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride), blocked cardiac acceleration caused by low frequency electrical stimulation of right postganglionic cardiac sympathetic nerve in dogs (with or without vagotomy), and slowed the heart rate by direct administration into the artery supplying the sinus node. In isolated rabbit hearts, clonidine also antagonized release of norepinephrine caused by electrical stimulation of intact sympathetic nerves (81). This inhibitory effect of clonidine on norepinephrine release was not due to its local anesthetic activity and was inversely related to overflow of norepinephrine caused by control electrical stimulation prior to administration of clonidine (82, 83). This negative correlation was thought to reflect competition between clonidine and liberated norepinephrine for a receptor site. On the basis of these findings, Starke hypothesized the existence of a presynaptic α-adrenergic receptor mediating feedback control of norepinephrine release (84). According to this concept, the release of norepinephrine by nerve impulses is inhibited by a feedback system; the feedback loop consists of released norepinephrine and α-adrenergic receptors on the nerve endings. α-Adrenergic antagonists block the access of norepinephrine and other α-stimulants to the receptors at the nerve membrane, thereby interrupting the feedback loop and facilitating the release of norepinephrine.

This concept of α-adrenergic receptor–mediated feedback control of norepinephrine release has been extended to central noradrenergic neurons. Clonidine was

found to diminish the stimulation-evoked tritium overflow from slices of rat cerebral cortex preincubated with ^{3}H-norepinephrine. The extent of this inhibition was greater at a low than at a high frequency of stimulation. α-Adrenergic blocking agents, phentolamine and phenoxybenzamine, increased the stimulation-induced release of norepinephrine from the cerebral cortical slices (85).

These observations raise the question as to the possible importance of prejunctional α-adrenergic receptors to the central hypotensive action of clonidine. The destruction of noradrenergic neurons by 6-hydroxydopamine reduced the hypotensive effect of clonidine in rabbits (86). In rats, however, Haeusler & Finch (87) found that 6-hydroxydopamine given i.c.v. did not alter the hypotensive effect of clonidine. In cats pretreated with reserpine and α-methyl-*p*-tyrosine at doses sufficient to produce marked depletion of norepinephrine in the central and peripheral nervous systems, clonidine produced its usual inhibitory effect on sympathetic nerve activity but higher doses were required (88).

Drugs Related to Clonidine

Among other α-adrenergic stimulants with central hypotensive activity, xylazine, 2-(2,6-dimethylphenylamino)-4H-5,6-dihydro-1,3-thiazine (Bayer 1470), is probably the most thoroughly investigated compound. In the initial pharmacological studies (89) xylazine inhibited the response to adrenergic as well as cholinergic nerve stimulation and had peripheral adrenergic stimulant and central hypotensive effects. It was also highly potent as an analgesic and sedative; as such it found application in veterinary medicine (90).

Central hypotensive activity was also observed in a series of oxazoline derivatives. The most active were Bay a6781, 2-[2-(e)-methyl-6(e)-methylcyclohexyl]-1-(e)-amino-2-oxazoline (91), and LD 2855, 2-(2,6-dimethylphenylamino)-1,3-oxazol-2-ine (92). The mechanism of their antihypertensive action appeared to be similar to clonidine.

Extensive pharmacological studies with guanabenz (WY 8678; BR 750; 2,6-dichlorobenzylideneamino guanidine acetate) indicated that this compound is also, in some respects, similar to clonidine. It was shown to lower arterial pressure by at least two mechanisms, i.e. centrally mediated reduction in sympathetic nerve activity and peripheral adrenergic neuron blockade (93–95).

Another α-adrenergic stimulant with antihypertensive activity is N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride or BS 100/141 (96). BS 100/141 was shown to have peripheral α-adrenergic stimulant action in cats, dogs, and rats. By infusion into the vertebral artery or by injection into the lateral cerebral ventricle of anesthetized cats, BS 100/141 produced a marked reduction in arterial pressure and heart rate at doses that were ineffective intravenously. BS 100/141 also reduced norepinephrine turnover rate in the brain stem of rats apparently by virtue of its α-adrenergic stimulant activity. The site of central antihypertensive action of BS 100/141 has been claimed to be different from clonidine. Clonidine reduced arterial pressure by topical application to the ventral surface of medulla oblongata of cats; under similar experimental conditions, BS 100/141 was ineffective.

Desipramine-Clonidine Interaction

Of considerable interest in relation to the site and the mechanism of hypotensive action of clonidine and of other α-adrenergic stimulants is the interaction between clonidine and desipramine, a tricyclic antidepressant and a neuronal uptake inhibitor of norepinephrine. According to Reid et al (97) the hypotensive activity of clonidine given intracisternally to rabbits was antagonized by desipramine. This interaction was confirmed in cats (98) and in man (99) but not in rabbits (100). Other tricyclic antidepressants also antagonized the hypotensive effects of clonidine in cats (98). The interaction of clonidine with desipramine is of clinical and also of theoretical significance. If inhibition of the uptake mechanism at the presynaptic sites of noradrenergic neurons is responsible for the interaction between clonidine and desipramine, a presynaptic site must be involved in the mode of antihypertensive action of clonidine.

CENTRAL β-ADRENERGIC RECEPTORS

Not only α- but also β-adrenergic receptors may be involved in the central regulation of arterial pressure. The presence of β-adrenergic receptors within the central nervous system was first suggested by Share & Melville (101) who found that intraventricular injection of the β-adrenergic blocking drug, dichloroisoproterenol (DCI) attenuated the cardiac acceleration resulting from an intraventricular injection of picrotoxin. Subsequently, a number of investigators demonstrated that isoproterenol, administered intraventricularly, will either raise or lower arterial pressure depending on the species and experimental conditions. Thus, in anesthetized cats (102), dogs (23, 103, 104), rabbits (28, 105, 106), and rats (107), an i.c.v. injection of isoproterenol has been reported to cause hypotension and tachycardia. Day & Roach (108), however, found that isoproterenol caused a pressor response and tachycardia in conscious cats. In a more extensive subsequent study (30), this effect was observed in only about one half of the cats examined; in the remaining animals, isoproterenol produced hypotension and tachycardia. A number of investigators have been able to block the effects of i.c.v. injections of isoproterenol by i.c.v. administration of β-adrenergic blocking agents (23, 30, 102, 105, 106, 108). The effects of isoproterenol are of central origin because section of the spinal cord (23, 102) and ganglion blockade (108) abolished the cardiovascular effects of i.c.v. injection of isoproterenol. Taken collectively, the available data indicate that centrally mediated cardiovascular effects of isoproterenol can be demonstrated in animals but the variability observed has not been satisfactorily explained.

Clinical studies have clearly demonstrated that β-adrenergic blocking drugs have antihypertensive activity. Early studies in man suggested that propranolol may have central nervous system side effects. A number of investigators tried to determine whether the central nervous system is involved in mediating the hypotensive effects of β-adrenergic blocking drugs. Kelliher & Buckley (109) were the first to provide evidence for a central site of action. Other workers, using various techniques and animal species, have observed a fall in arterial pressure after central administration

of β-adrenergic blocking drugs (30, 106, 108, 110, 111). The usual response to an i.c.v. injection of a β-adrenergic blocking agent is a transient rise in arterial pressure followed by a sustained fall. This early rise in arterial pressure has been attributed to the local anesthetic action of β-adrenergic blocking drugs (105, 106) but hypertensive response to timolol i.c.v. (110), a β-adrenergic blocking agent devoid of local anesthetic properties, has also been observed. Reports on the cardiovascular effects of vertebral artery injections of propranolol are conflicting (111, 112). Stern et al (111) observed a difference between intravenous versus intravertebral injections of propranolol, but Offerhaus & Van Zwieten (112) found similar hypotensive effects regardless of which route of administration was used. It has not been clearly shown that the cardiovascular effects of centrally administered propranolol are mediated through central noradrenergic neurons. However, according to one report (105), propranolol administered i.c.v. does not produce a fall in arterial pressure in rabbits pretreated with intracisternal 6-hydroxydopamine, an observation suggesting that noradrenergic neurons must be intact for the drug to exert its central hypotensive effect.

CONCLUSIONS

In recent years, it has become apparent that central noradrenergic neurons are involved in the regulation of arterial pressure. Areas in the central nervous system known to be involved in the control of arterial pressure and heart rate are densely innervated by noradrenergic neurons. Destruction of these neurons with 6-hydroxydopamine prevents the development of certain forms of hypertension in animals. Noradrenergic control of arterial pressure is mediated at least partially through central α-adrenergic receptors. β-Adrenergic receptors in the central nervous system have been identified, but their importance in the regulation of arterial pressure remains to be defined. The main site of antihypertensive action of methyldopa and clonidine is the central nervous system. The evidence suggests that their effects are mediated through α-adrenergic receptors at a pre- or postsynaptic site.

Further understanding of central noradrenergic control of arterial pressure will provide a basis for development of novel and more selective antihypertensive drugs.

Literature Cited

1. Dahlström, A., Fuxe, K. 1964. *Acta Physiol. Scand.* 62:Suppl. 232, 1–55
2. Ungerstedt, U. 1971. *Acta Physiol. Scand.* 82:Suppl. 367, 1–48
3. Bolme, P., Fuxe, K., Lidbrink, P. 1972. *Res. Commun. Chem. Pathol. Pharmacol.* 4:657–97
4. Dahlström, A., Fuxe, K. 1965. *Acta Physiol. Scand.* 64:Suppl. 247, 1–36
5. Lindvall, O., Björklund, A. 1974. *Acta Physiol. Scand.* 92:Suppl. 412, 1–48
6. Fuxe, K. 1965. *Acta Physiol Scand.* 64:Suppl. 247, 37–85
7. Crill, W. E., Reis, D. J. 1968. *Am. J. Physiol.* 214:269–76
8. Hökfelt, T., Fuxe, K., Goldstein, M. 1973. *Brain Res.* 62:461–69
9. Hökfelt, T., Fuxe, K., Goldstein, M., Johansson, O. 1973. *Acta Physiol. Scand.* 89:286–88
10. Hökfelt, T., Fuxe, K., Goldstein, M., Johansson, O. 1974. *Brain Res.* 66: 235–51
11. Saavedra, J. M., Palkovits, M., Brownstein, M. J., Axelrod, J. 1974. *Nature London* 248:695–96
12. Koslow, S. H., Schlumpf, M. 1974. *Nature London* 251:530–31
13. Reis, D. J., Doba, N. 1974. *Prog. Cardiovasc. Dis.* 17:51–71

14. Chalmers, J. P. 1975. *Circ. Res.* 36:469–80
15. Doba, N., Reis, D. J. 1973. *Circ. Res.* 32:584–93
16. Doba, N., Reis, D. J. 1974. *Circ. Res.* 34:293–301
17. Chalmers, J. P., Reid, J. L. 1972. *Circ. Res.* 31:789–804
18. Haeusler, G., Finch, L., Thoenen, H. 1972. *Experientia* 28:1200–1203
19. Lewis, P. J., Reid, J. L., Chalmers, J. P., Dollery, C. T. 1973. *Clin. Sci. Mol. Med.* 45:115S–18S
20. Severs, W. B., Daniels—Severs, A. E. 1973. *Pharmacol. Rev.* 25:415–49
21. McCubbin, J. W., Kaneko, Y., Page, I. H. 1960. *Circ. Res.* 8:849–58
22. Kaneko, Y., McCubbin, J. W., Page, I. H. 1960. *Circ. Res.* 8:1228–34
23. Bhargava, K. P., Mishra, N., Tangri, K. K. 1972. *Br. J. Pharmacol.* 45:596–602
24. Nashold, B. S., Mannarino, E., Wunderlich, M. 1962. *Nature London* 193:1297–98
25. Share, N. N., Melville, K. I. 1963. *J. Pharmacol. Exp. Ther.* 141:15–21
26. Smookler, H. H., Severs, W. B., Kinnard, W. J., Buckley, J. P. 1966. *J. Pharmacol. Exp. Ther.* 153:485–94
27. Baum, T., Shropshire, A. T. 1973. *Neuropharmacology* 12:49–56
28. Toda, N., Matsuda, Y., Shimamoto, K. 1969. *Int. J. Neuropharmacol.* 8:451–61
29. Heise, A., Kroneberg, G. 1972. *Eur. J. Pharmacol.* 17:315–17
30. Day, M. D., Roach, A. G. 1974. *Br. J. Pharmacol.* 51:325–33
31. Struyker Boudier, H. A. J., Smeets, G. W. M., Brouwer, G. M., van Rossum, J. M. 1974. *Neuropharmacology* 13: 837–46
32. Struyker Boudier, H., Smeets, G., Brouwer, G., van Rossum, J. 1974. *Life Sci.* 15:887–99
33. Struyker Boudier, H. A. J., Bekers, A. 1975. *Eur. J. Pharmacol.* 31:153–55
34. De Jong, W. 1974. *Eur. J. Pharmacol.* 29:179–81
35. Neumayr, R. J., Hare, B. D., Franz, D. N. 1974. *Life Sci.* 14:793–806
36. Chalmers, J. P., Wurtman, R. J. 1971. *Circ. Res.* 28:480–91
37. Coote, J. H., Macleod, V. H. 1974. *J. Physiol.* 241:453–75
38. De Jong, W., Zandberg, P., Bohus, B. 1975. *Prog. Brain Res.* 42:In press
39. Van Zwieten, P. A. 1973. *J. Pharm. Pharmacol.* 25:89–95
40. Day, M. D., Roach, A. G. 1974. *Clin. Exp. Pharmacol. Physiol.* 1:347–60
41. Carlsson, A., Lindqvist, M. 1962. *Acta Physiol. Scand.* 54:87–94
42. Henning, M., Van Zwieten, P. A. 1968. *J. Pharm. Pharmacol.* 20:409–17
43. Henning, M. 1969. *Acta Pharmacol. Scand.* 27:135–48
44. Henning, M., Rubenson, A. 1971. *J. Pharm. Pharmacol.* 23:407–11
45. Day, M. D., Roach, A. G., Whiting, R. L. 1973. *Eur. J. Pharmacol.* 21: 271–80
46. Torchiana, M. L., Lotti, V. J., Clark, C. M., Stone, C. A. 1973. *Arch. Int. Pharmacodyn. Ther.* 205:103–13
47. Heise, A., Kroneberg, G. 1973. *Arch. Pharmacol.* 279:285–300
48. Struyker Boudier, H., Smeets, G., Brouwer, G., van Rossum, J. M. 1975. *Arch. Int. Pharmacodyn. Ther.* 213: 285–93
49. De Jong, W., Nijkamp, F. P., Bohus, B. 1975. *Arch. Int. Pharmacodyn. Ther.* 213:272–84
50. Finnerty, F. A., Buchholz, J. H., Guillaudeu, R. L. 1957. *Proc. Soc. Exp. Biol. Med.* 94:376–79
51. Hutcheon, D. E., P'an, S. Y., Gardocki, J. F., Jaeger, D. A. 1955. *J. Pharmacol. Exp. Ther.* 113:341–52
52. Hutcheon, D. E., Scriabine, A., Niesler, V. N. 1958. *J. Pharmacol. Exp. Ther.* 122:101–9
53. Hutcheon, D. E., Scriabine, A., Ling, J. S., P'an, S. Y., Bloom, B. M. 1964. *Arch. Int. Pharmacodyn. Ther.* 147: 146–55
54. Hoefke, W., Kobinger, W. 1966. *Arzneim. Forsch.* 16:1038–50
55. Van Zwieten, P. A. 1968. *Klin. Wochenschr.* 46:77–80
56. Schmitt, H., Schmitt, H., Boissier, J. R., Giudicelli, J. F. 1967. *Eur. J. Pharmacol.* 2:147–48
57. Sattler, R. W., Van Zwieten, P. A. 1967. *Eur. J. Pharmacol.* 2:9–13
58. Constantine, J. W., McShane, W. K. 1968. *Eur. J. Pharmacol.* 4:109–23
59. Schmitt, H., Schmitt, H., Boissier, J. R., Giudicelli, J. F., Fichelle, J. 1968. *Eur. J. Pharmacol.* 2:340–46
60. Sherman, G. P., Grega, G. J., Woods, R. J., Buckley, J. P. 1968. *Eur. J. Pharmacol.* 2:326–28
61. Toda, N., Fukuda, N., Shimamoto, K. 1969. *Jpn. J. Pharmacol.* 19:199–210
62. Schmitt, H., Schmitt, H., Fénard, S. 1971. *Eur. J. Pharmacol.* 14:98–100
63. Schmitt, H., Schmitt, H. 1970. *Eur. J. Pharmacol.* 9:7–13
64. Anden, N. E., Corrodi, H., Fuxe, K.,

Hökfelt, B., Hökfelt, T., Rydin, C., Svensson, T. 1970. *Life Sci.* 9:513–24
65. Robson, R. D., Kaplan, H. R., Laforce, S. 1969. *J. Pharmacol. Exp. Ther.* 169:120–31
66. Robson, R. D., Kaplan, H. R. 1969. *Eur. J. Pharmacol.* 5:328–37
67. Nayler, W. G., Stone, J. 1970. *Eur. J. Pharmacol.* 10:161–67
68. Korner, P. I., Oliver, J. R., Sleight, P., Chalmers, J. P., Robinson, J. S. 1974. *Eur. J. Pharmacol.* 28:189–98
69. Haeusler, G. 1973. *Arch. Pharmacol.* 278:231–46
70. Kobinger, W., Walland, A. 1972. *Eur. J. Pharmacol.* 19:203–9
71. Kobinger, W., Walland, A. 1972. *Eur. J. Pharmacol.* 19:210–17
72. Schmitt, H., Schmitt, H., Fénard, S. 1973. *Experientia* 29:1247–49
73. Bousquet, P., Guertzenstein, P. G. 1973. *Br. J. Pharmacol.* 49:573–79
74. Sinha, J. N., Atkinson, J. M., Schmitt, H. 1973. *Eur. J. Pharmacol.* 24:113–19
75. Klevans, L. R., Kepner, K., Kovacs, J. L. 1973. *Eur. J. Pharmacol.* 24: 262–65
76. Bolme, P., Fuxe, K. 1971. *Eur. J. Pharmacol.* 13:168–74
77. Bloch, R., Bousquet, P., Feldman, J., Velly, J., Schwartz, J. 1974. *Thérapie* 29:251–59
78. Finch, L., Buckingham, R. E., Moore, R. A., Bucher, T. J. 1975. *J. Pharm. Pharmacol.* 27:181–86
79. Scriabine, A., Stavorski, J., Wenger, H. C., Torchiana, M. L., Stone, C. A. 1970. *J. Pharmacol. Exp. Ther.* 171: 256–64
80. Scriabine, A., Stavorski, J. M. 1973. *Eur. J. Pharmacol.* 24:101–4
81. Starke, K., Schümann, H. J. 1971. *Experientia* 27:70–71
82. Starke, K., Wagner, J., Schümann, H. J. 1972. *Arch. Int. Pharmacodyn. Ther.* 195:291–308
83. Starke, K., Altmann, K. P. 1973. *Neuropharmacology* 12:339–47
84. Starke, K. 1973. *Frontiers in Catecholamine Research,* ed. E. Usdin, S. Snyder, 561–65. New York: Pergamon
85. Starke, K., Montel, H. 1973. *Neuropharmacology* 12:1073–80
86. Dollery, C. T., Reid, J. L. 1973. *Br. J. Pharmacol.* 47:206–16
87. Haeusler, G., Finch, L. 1972. *J. Pharmacol.* 3:544–45
88. Haeusler, G. 1974. *Arch. Pharmacol.* 286:97–111
89. Kroneberg, G., Oberdorf, A., Hoffmeister, F., Wirth, W. 1967. *Arch. Pharmacol.* 256:257–80
90. Simon, P., Chermat, R., Puech, A. J., Goujet, M. A., Boissier, J. R. 1973. *Thérápie* 28:735–51
91. Jacobs, F., Werner, U., Schümann, H. J. 1972. *Arzneim Forsch.* 22: 1124–26
92. Giudicelli, R., Schmitt, H. 1970. *J. Pharmacol.* 1:339–58
93. Baum, T. et al 1969. *Experientia* 25:1066–67
94. Baum, T. et al 1970. *J. Pharmacol. Exp. Ther.* 171:276–87
95. Baum, T., Shropshire, A. T. 1970. *Neuropharmacology* 9:503–6
96. Scholtysik, G., Jerie, P. 1976. *New Antihypertensive Drugs,* ed. A. Scriabine, C. S. Sweet. Holliswood, NY: Spectrum. In press
97. Reid, J. L., Briant, R. H., Dollery, C. T. 1973. *Life Sci.* 12:459–67
98. Van Spanning, H. W., Van Zwieten, P. A. 1973. *Eur. J. Pharmacol.* 24: 402–4
99. Briant, R. H., Reid, J. L., Dollery, C. T. 1973. *Br. Med. J.* 1:522–23
100. Hoefke, W., Warnke-Sachs, E. 1974. *Arzneim. Forsch.* 24:1046–47
101. Share, N. N., Melville, K. I. 1965. *Int. J. Neuropharmacol.* 4:149–56
102. Gagnon, D. J., Melville, K. I. 1967. *Int. J. Neuropharmacol.* 6:245–51
103. Schmitt, H., Fénard, S. 1971. *Arch. Int. Pharmacodyn. Ther.* 190:229–40
104. Conway, E. L., Lang, W. J. 1974. *Clin. Exp. Pharmacol. Physiol.* 1:59–64
105. Myers, M. G., Lewis, P. J., Reid, J. L., Dollery, C. T. 1975. *Neuropharmacology* 14:221–26
106. Reid, J. L., Lewis, P. J., Myers, M. G., Dollery, C. T. 1974. *J. Pharmacol. Exp. Ther.* 188:394–99
107. Ito, A., Schanberg, S. M. 1974. *J. Pharmacol. Exp. Ther.* 189:392–404
108. Day, M. D., Roach, A. G. 1973. *Nature London New Biol.* 242:30–31
109. Kelliher, G. J., Buckley, J. P. 1970. *J. Pharm. Sci.* 59:1276–80
110. Sweet, C. S., Scriabine, A., Wenger, H. C., Ludden, C. T., Stone, C. A. 1976. *Regulation of Blood Pressure by the Central Nervous System,* ed. G. Onesti, M. Fernandes, K. Kim. New York: Grune & Stratton. In press
111. Stern, S., Hoffman, M., Braun, K. 1971. *Cardiovasc. Res.* 5:425–30
112. Offerhaus, L., Van Zwieten, P. A. 1974. *Cardiovasc. Res.* 8:488–95