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THE CENTRAL NORADRENERGIC TRANSMISSION AND THE LOCUS COERULEUS: A REVIEW OF THE DATA, AND THEIR IMPLICATIONS FOR NEUROTRANSMISSION AND NEUROMODULATION

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Contents

1. The Locus Coeruleus and Neurotransmission

1.1. Introduction

Since the discovery that the locus coeruleus (LC) contains the greatest number of norepinephrine-containing cells (NE cells) in the central nervous system (CNS), and has by far the most extended target region in the CNS of all central NE cells groups (Dahlström and Fuxe, 1964; Swanson and Hartman, 1975), very many investigations have been devoted to this small nucleus (reviews e.g. Amaral and Sinnamon, 1977; Clark, 1979; Ramm, 1979; McNaughton and Mason, 1980; Van Dongen, 1980). As a consequence of these investigations much knowledge has accumulated on the morphology of the LC cells and their terminals, and on the central NE transmission, such that the LC is an often used illustrative example in discussions on neurotransmission and neuromodulation (e.g. Dismukes, and commentaries, 1979). In this paper I intend to review the data found in the literature on the central NE transmission which are relevant for the molecular mechanism of NE- induced effects, and for the question on whether NE is an efferent neurotransmitter (or an efferent neuromodulator) of the LC (cf. also Szabadi, 1979; and Woodward, 1979). The implications of these findings for the general discussion on neurotransmission and neuromodulation will be mentioned; their implications for the 'function' of the LC are mentioned elsewhere (Van Dongen, 1980, pp 137–143).

1.2. Definition of the LC

In this paper "locus coeruleus" is used as a collective term for the catecholamine-containing cells (CA-cells) in the dorsolateral pontine tegmentum of mammals. General statements on a brain region are only meaningful when this region is a single entity (or "functional system") (cf. Van Dongen 1980, pp. 217–266); under the above mentioned

definition, the LC seems to be an entity, and a further subdivision of the LC (cf. Amaral and Sinnamon, 1977; Grzanna and Molliver, 1980) need not to be made in this paper, because the parts of the LC seem to be similar under the aspect of the NE transmission. An implication of this definition is, that cells containing other putative neurotransmitters found in the region of the LC will not be taken into consideration, because no indications have been published in favour of a "co-existence" of these putative neurotransmitters and NE in a single cell. These compounds are serotonin (5-HT; Sladek and Walker, 1977; Pickel *et al.*, 1977a, Legér *et al.*, 1978a), substance *P* (Ljungdahl *et al.*, 1978a) and neurotensin (Uhl *et al.*, 1979b), while also a number of small non-NE cells in the region of the LC have been described (Ramon-Moliner 1974; Swanson 1976b; Shimizu *et al.*, 1978, 1979).

1.3. Definitions in Neurochemistry

Many lists of criteria for identifying a compound as a neurotransmitter, neuromodulator, neurohormone and so on have been published (cf. Werman, 1966; Florey, 1967; Davidson, 1976; Torda, 1977a; Barchas *et al.*, 1978; Orrego, 1979; Iversen, 1979; Dismukes and commentaries 1979). Given the incomplete knowledge on this subject, a classification of neuroactive compounds must be flexible (Dismukes 1979), but the words used must also be sharply defined, when one wants to make informative and falsificable statements. In the first part of this paper, the words "neurotransmitter" and "(non)synaptic neurotransmitter" will be used as defined below (somewhat in line with Dismukes 1979), while in the latter part some comments on "neurotransmission" and "neuromodulation" will be made.

1.4. Definition of "Neurohumor"

Compound *C* is a "neurohumor" of neuron *N* (or group of neurons *N*), when the following statements are confirmed experimentally:

1. *C* is present in neuron *N*.
2. *C* is synthetized by neuron *N*.
3. Electrical stimulation of neuron *N* causes secretion (release) of *C*.
4. *C* interacts with specific sites of action (receptors).
5. At least one system exists which terminates the effect of *C* at its target site.
6. Direct application of *C* mimics the effect of increasing its endogenous concentration; this effect is identical in all respects, including pharmacological.

1.5. Definition of "Neurotransmitter"

Compound *C* is a "neurotransmitter" of neuron *N*, when the following statements are confirmed experimentally:

1. *C* is a neurohumor.
2. The site of release of *C* is relatively close to its site of action, and *C* is not transported to its site of action by the cerebrospinal fluid (CSF) nor the blood.

Note that under this definition, the concept "neurotransmitter" also includes what many authors call "neuromodulator" (Torda, 1977a; Barchas *et al.*, 1978; commentaries in Dismukes, 1979). The concept "neuromodulator" as used by Florey (1960, see also commentary in Dismukes 1979) and Orrego (1979) is not included; a "neuromodulator" as defined by these authors might be released (1) independently from a neuron's firing rate, and (2) also by elements other than neurons.

1.6. Definitions of "(non)synaptic Neurotransmitter"

Compound *C* is a "synaptic neurotransmitter" of neuron *N*, when the following statements are confirmed experimentally:

1. *C* is a neurotransmitter.

2. *C* is present in the presynaptic part of a morphologically identified specialized synapse (cf. Cobb and Penthreath, 1978, Fig. 5a–g). *C* acts transsynaptically: the target site (receptor) of *C* is located in the postsynaptic membrane.

Compound *C* is a "nonsynaptic neurotransmitter" of neuron *N*, when the following statements are confirmed experimentally:

1. *C* is a neurotransmitter.
2. *C* is present in non-synaptic terminals, i.e. terminals without synaptic specializations (Cobb and Penthreath, 1978, Fig. 5h).

Note that under this definition, "synaptic neurotransmitter" is a broader concept than "neurotransmitter" as used by Barchas *et al.* (1978); according to the latter authors the action of a "neurotransmitter" must be reflected as excitatory or inhibitory post-synaptic potentials. The "nonsynaptic neurotransmitters", as defined above and by Dismukes (1979), are partly overlapping with the "neuromodulators" according to Barchas *et al.* (1978); a "nonsynaptic neurotransmitter" is released from a neuron, while a "neuromodulator" according to Barchas *et al.* (1978) might be released from other elements; moreover, a "neuromodulator" is said to have "neuronal effects", so its target elements probably must be neurons, while the target elements of a "nonsynaptic neurotransmitter" are left unspecified.

1.7. Definition of Neurohormone

Compound *C* is a "neurohormone" of neuron *N*, when the following statements are confirmed experimentally:

1. *C* is a neurohumor.
2. The site of release of *C* is remote from its site of action; *C* is transported to its site of action by the CSF and/or the blood.

2. Is NE a Neurotransmitter of the LC?

2.1. Presence of NE

2.1.1. *Overall pattern of NE distribution*

Abundant evidence has been presented that NE is present in the cell bodies, dendrites, axons, varicosities and synapses of the LC cells of the rat (Amaral and Sinnamon, 1977). In all mammals investigated a CA-containing presumed homologue of the rat's LC has been found, and this CA has been demonstrated to be NE both in the cat and in man (Jones *et al.* 1977a; Farley and Hornykiewicz, 1977, Marchand *et al.*, 1979a, b). NE is transported somatofugally from the LC cells bodies (Levin *et al.*, 1976, Levin and Stolk, 1977). At the moment, the presence of NE in the cell bodies, varicosities and synapses of the LC in the rat is generally accepted. The presence of NE (as revealed by histofluorescence) has been used in mapping studies of the efferent fibers of the LC (e.g. Ungerstedt, 1971a; Lindvall and Bjorklund, 1974), and the decrease in telencephalic NE after a lesion of the LC has been used to check the completeness of the lesion (cf. references in Clark, 1979; Mason, 1979).

2.1.2. *Do the varicosities release NE?*

The axons of the LC cells are beaded fibers consisting of varicosities and thin intervaricose segments (Descarries *et al.*, 1977; Beaudet and Descarries, 1978). I have three reasons to suppose that NE is released from these varicosities (cf. Beaudet and Descarries, 1978).

1. The varicosities contain NE (Dahlström and Fuxe, 1964; Lindvall and Bjorklund,

1974) and vesicles with the appearance of exocytotic ("synaptic") vesicles (Hökfelt *et al.*, 1968; Swanson *et al.*, 1977; Descarries *et al.*, 1977; Sakumoto *et al.*, 1977; Koda *et al.*, 1978a, b; Zecevic and Molliver, 1978; Beaudet and Descarries, 1978).

2. The varicosities contain immunoreactive dopamine-β-hydroxylase (DBH) (Swanson and Hartman 1975; Lundberg *et al.*, 1977; Cimarusti *et al.*, 1979), and therefore probably have a synthetic system for NE.

3. The varicosities accumulate exogenous ^{3}H-NE (Descarries *et al.*, 1977) and other CAs (5-OHDA, Zecevic and Molliver, 1978), and therefore probably have a specialized re-uptake system for NE.

The varicosities share these 3 properties with classical synaptic boutons; therefore they probably release NE. Although such non-synaptic release of NE has not been definitively demonstrated, it is assumed that the varicosities of central NE fibers are terminals further in this paper, as has been suggested for peripheral NE fibers (Haefely 1972).

2.1.3. *The occurrence of free LC endings*

The frequent occurrence of large numbers of NE terminals without synaptic specializations in LC target regions has been described by authors using various techniques to identify NE terminals (Amaral and Sinnamon, 1977; Descarries *et al.*, 1977; Swanson *et al.*, 1977; Sakumoto *et al.*, 1977; Koda *et al.*, 1978a, b; Cimarusti, 1979; Ouimet, 1979; Beaudet and Descarries, 1978; but not by Zecevic and Molliver, 1978). The similarities between the NE terminals of the peripheral sympathetic system and of the LC terminals has been noted (Amaral and Sinnamon, 1977; Descarries *et al.*, 1977; Koda and Bloom, 1977; Koda *et al.*, 1978b). Note that this implies that the words "presynaptic" and "postsynaptic" are inadequate for the NE transmission; instead of these words, "of the terminal" and "of the target cell" will be used respectively.

2.1.4. *LC terminals on neurons, synapses*

In all LC terminal regions investigated some NE terminals are described as being in close contacts with neuronal somata and dendrites. In the cerebellum and the hippocampus, these contacts are predominantly on the Purkinje and pyramidal cells respectively (Swanson and Hartman, 1975; Amaral and Sinnamon, 1977; Loy *et al.*, 1980), while the NE terminals in the spinal cord and neocortex are found on various morphological types of neurons (Amaral and Sinnamon 1977; Jordan *et al.*, 1977). Some NE terminals have synaptic specializations (Nelson *et al.*, 1973, Descarries *et al.*, 1977; Koda *et al.*, 1978a, b; Zecevic and Molliver, 1978; Beaudet and Descarries, 1978; Cimarusti *et al.*, 1979); these synapses were found to be either symmetrical or asymmetrical synapses on dendrites or somata.

2.1.5. *LC terminals on cerebral blood vessels*

The cerebral blood vessels receive NE terminals from the ganglion cervicale superius and from central NE cells. The endings of the ganglion cervicale superius terminate on large vessels, and the LC terminals are contiguous for some distance with the small cerebral blood vessels (Amaral and Sinnamon, 1977; Itakura *et al.*, 1977; De Witt, 1978). The proportion of the LC terminals, however, that end on cerebral capillaries is small (Itakura *et al.*, 1977). The ultrastructure of the LC terminals on small blood vessels indicates that these terminals indeed affect the blood vessels (Swanson *et al.*, 1977; Itakura *et al.*, 1977; but not Edvinsson and MacKenzie, 1977).

2.1.6. *NE terminals on other CNS elements*

NE terminals have been described in the eminentia mediana, which receives an LC input (Palkovits *et al.*, 1977b; Zàborsky *et al.*, 1977), as being in close contact with ependymal cells, neurosecretory fibers and other axons; no NE terminals with synaptic specializations have been found here (Sakumoto *et al.*, 1977). Similar NE terminals have

been found in the area postrema (Torack *et al.*, 1973), but it is questionable whether their origin is the LC. It is possible that NE released from these terminals reaches the ventricle (cf. Adèr *et al.*, 1979; Perlow *et al.*, 1980).

2.2. SYNTHESIS OF NE

The enzymes necessary for the synthesis of NE are present in the LC. Tyrosine hydroxylase (TH) is demonstrated enzymatically in the LC region (Saito *et al.*, 1977a; Bullard *et al.*, 1978), and immunohistochemically in the LC bodies (Hökfelt *et al.*, 1976; Nagatsu *et al.*, 1979a). Immunoreactive DBH is present in the LC cells bodies, axons and terminals (Hartman and Udenfriend 1972; Swanson and Hartman 1975; Grzanna *et al.*, 1977, 1978; Cimarusti *et al.*, 1979; Nagatsu *et al.*, 1979a); the presence of immunoreactive or enzymatically active DBH has been used in mapping studies of the LC efferents (Ross and Reis 1974; Swanson and Hartman 1975). Immunoreactive DBH is present in small vesicles with the appearance of exocytotic ("synaptic") vesicles, as in large ones (Lundberg *et al.*, 1977; Cimarusti *et al.*, 1979). DBH has been reported as being present in all vesicles of a DBH-positive terminal, so that single vesicles would contain both NE and DBH (Lundberg *et al.*, 1977), but this is still the subject of discussion (Cimarusti *et al.*, 1979). Other substances probably related to the synthesis of NE are also present in the LC: copper (Yoshinaga and Shimizu, 1968; cf. Friedman and Kaufman, 1965; Molinoff *et al.*, 1971; Lander and Austin 1976), vitamin A (Iijima 1977, 1978) and reduced pterins (Bullard *et al.*, 1978). Moreover, ^{3}H-DA injected into the LC region is converted into ^{3}H-NE, and transported somatofugally (Levin *et al.*, 1976; Levin and Stolk, 1977).

2.3. RELEASE OF NE

2.3.1. *Experimentally induced NE release*

Only in one *in vivo* study (Tanaka *et al.*, 1976) has a direct measurement of the NE release after the electrical stimulation of the LC been described; NE release was measurable only in the presence of an NE uptake inhibitor (desipramine). The *in vivo* release of NE by electrical stimulation of the LC has been measured indirectly as an increase in the levels of 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), the main metabolite of central NE (Korf *et al.*, 1973a; Crawley *et al.*, 1978, 1979a; cf. Rutledge and Johanson, 1967; Schanberg *et al.*, 1968). Release of central NE can be increased *in vitro* by depolarizing manipulations (electrical stimulation or K^{+}-ions) or by amphetamine (Dismukes and Mulder, 1976; Dismukes *et al.*, 1977; Lane and Aprison, 1977; Kant and Meyerhoff, 1977a, 1978; Rutledge, 1978).

2.3.2. *Release into the ventricle?*

The NE content of the cerebrospinal fluid (CSF) is highest during awake periods (Ziegler *et al.*, 1976; Perlow *et al.*, 1978), when also the LC cells' firing rate is highest (Foote *et al.*, 1980). The CSF NE is most probably (at least partly) released by LC neurons, since (1) the CSF NE is of central and not of peripheral origin (Ziegler *et al.*, 1977a, Perlow et al., 1978), and (2) HRP-labeled LC cells have been found after injection of HRP into the lateral ventricle (Adèr *et al.*, 1979).

2.4. INACTIVATION AFTER RELEASE

2.4.1. *Introduction*

The action of a neurotransmitter must after a while come to an end; this termination of action can be accomplished in 3 different ways:

1. Uptake of the compound by cells (usually the cell from which it was released, re-uptake), thereby removing it from its site of action.
2. Metabolic conversion of the compound into metabolites which are inactive, or have at least a different action.
3. Diffusion of the compound away from the site of action.

TABLE 1. EFFECTS OF ELECTRICAL STIMULATION OF THE LC AND OF IONTOPHORETICAL APPLICATION OF NE ON THE SAME CELLS (FOR REFERENCES SEE BELOW)

	Effects	References
Membrane potential	hyperpolarization	39
This hyperpolarization is:		
reduced by	prostaglandines (E)	39
enhanced by	papaverine	39
Membrane resistance	increase	39
1. NE/LC-induced suppression		39, 47, 48, 57, 89, 96, 146, 148
This suppression is:		
antagonized by	β-blocking agents	27, 47, 48, 57, 96, 146
reduced by	prostaglandines (E)	39, 47, 48
	glycoprotein	89
	lithium ions	148
enhanced by	papaverine	39, 47, 48
	desipramine	47, 48
Response to stimuli	reduced	146, 161
2. NE/LC-induced activation		182
This activation is:		
antagonized by	α-blocking agents	182
Response to stimuli	enhanced	182

Key to the references in the tables 1 and 2, effects of the LC and of NE on single unit activity, and its mechanism (for earlier articles see the review of Salmoiraghi 1966).

1. Engberg and Ryall, 1966; 2. Weight and Salmoiraghi, 1966a; 3. Weight and Salmoiraghi, 1966b; 4. Biscoe *et al.*, 1966; 5. Avanzino *et al.*, 1966; 6. Legge *et al.*, 1966; 7. Weight and Salmoiraghi, 1967; 8. Yamamoto, 1967; 9. Phillis and York, 1967; 10. Tebecis, 1967; 11. Phillis *et al.*, 1968a; 12. Boakes *et al.*, 1968a; 13. Phillis *et al.*, 1968b; 14. Roberts and Straughan, 1968; 15. Johnson *et al.*, 1969a; 16. Johnson *et al.*, 1969b; 17. Engberg and Thaller, 1970; 18. Engberg and Marshall, 1971; 19. Hösli *et al.*, 1971; 20. Boakes *et al.*, 1971; 21. Gonzales-Vegas, 1971; 22. Gonzales-Vegas and Wolstencroft, 1971a; 23. Gonzales-Vegas and Wolstencroft, 1971b; 24. Siggins *et al.*, 1971a; 25. Siggins *et al.*, 1971b; 26. Hoffer *et al.*, 1971a; 27. Hoffer *et al.*, 1971b; 28. Godfraind and Pumain, 1971; 29. Siggins *et al.*, 1971c; 30. Stone, 1971; 31. Frederickson *et al.*, 1971; 32. Boakes *et al.*, 1972; 33. Godfraind and Pumain, 1972; 34. Frederickson *et al.*, 1972; 35. Stone, 1972; 36. Engberg and Marshall, 1973; 37. Sasa and Takaori, 1973; 38. Anderson *et al.*, 1973; 39. Hoffer *et al.*, 1973; 40. Stone, 1973; 41. Nelson *et al.*, 1973; 42. Sasa *et al.*, 1974a; 43. Sasa *et al.*, 1974b; 44. Boakes *et al.*, 1974; 45. Lake and Jordan, 1974; 46. Nakai and Takaori, 1974; 47. Segal and Bloom, 1974a; 48. Segal and Bloom, 1974b; 49. Segal, 1974; 50. Phillis, 1974a, 51. Phillis, 1974b; 52. Phillis and Limacher, 1974; 53. Yarbrough *et al.*, 1974; 54. Bevan *et al.*, 1974a; 55. Bevan *et al.*, 1974b; 56. Sasa *et al.*, 1975; 57. Freedman and Hoffer, 1975; 58. Foote *et al.*, 1975; 59. Gilbert *et al.*, 1975; 60. Phillis *et al.*, 1976; 61. Jordan and McCrea, 1976; 62. Kirsten and Sharma, 1976; 63. Sasa *et al.*, 1976; 64. Freedman *et al.*, 1976, 65. Siggins *et al.*, 1976; 66. Nathanson *et al.*, 1976; 67. Galaher and Aghajanian, 1976; 68. Wang *et al.*, 1976; 69. Bunney and Aghajanian, 1976a; 70. Bunney and Aghajanian, 1976b; 71. Segal and Bloom, 1976a; 72. Segal and Bloom, 1976b; 73. Segal, 1976; 74. Vetulani *et al.*, 1976a; 75. Vetulani *et al.*, 1976b; 76. Skolnick and Daly, 1976a; 77. Skolnick and Daly, 1976b; 78. Yarbrough, 1976; 79. Gähwiler, 1976; 80. Ahn *et al.*, 1976; 81. Cedarbaum and Aghajanian, 1976; 82. Bockaert *et al.*, 1977; 83. Bonkowski and Dryden, 1977; 84. Jordan *et al.*, 1977; 85. Sasa *et al.*, 1977a; 86. Freedman *et al.*, 1977; 87. Wise and Hoffer, 1977; 88. Nathanson, 1977; 89. Torda, 1977; 90. Harden *et al.*, 1977; 91. Vetulani *et al.*, 1977; 92. Anderson *et al.*, 1977; 93. Sasa *et al.*, 1977b; 94. Bevan *et al.*, 1977; 95. Sharma, 1977; 96. Phillis and Kostopoulos, 1977; 97. Iversen, 1977; 98. Nathanson, 1977; 99. Rasmussen and Goodman, 1977; 100. Desaiah and Ho, 1977; 101. Nishino and Koizumi, 1977; 102. Cedarbaum and Aghajanian, 1977; 103. Aghajanian *et al.*, 1977; 104. Stone and Taylor, 1977; 105. Headley *et al.*, 1978; 106. Krnjević *et al.*, 1978; 107. Sinnamon, 1978; 108. Taylor *et al.*, 1978; 109. Takemoto *et al.*, 1978, 110. Nishino and Koizumi, 1978; 111. Torda, 1978; 112. Winokur and Beckman, 1978; 113. Perkins and Whitehead, 1978; 114. Finch *et al.*, 1978; 115. Dillier *et al.*, 1978; 116. Stone and Taylor, 1978a; 117. Stone and Taylor, 1978b; 118. Stone and Taylor, 1978c; 119. Stone and Taylor, 1978d; 120. Ewart and Logan, 1978a; 121. Ewart and Logan, 1978b; 122. Ewart and Logan, 1978c; 123. Hicks and McLennan, 1978; 124. Reader, 1978; 125. Bevan *et al.*, 1978a; 126. Bevan *et al.*, 1978b; 127. Harris, 1978; 128. Jones, 1978; 129. Hauser, 1978; 130. Robinson, 1978; 131. Skolnick *et al.*, 1978a; 132. Skolnick *et al.*, 1978b; 133. Reches, 1978; 134. Nimitkitpaisan and Skolnick, 1978; 135. Tsang and Lal, 1978; 136. Tsang *et al.*, 1978; 137. Wu and Phillis, 1978; 138. Schaefer *et al.*, 1978; 139. Belcher *et al.*, 1978; 140. Cedarbaum and Aghajanian, 1978; 141.

2.4.2. *Re-uptake*

Re-uptake is the main cause of inactivation of released central NE (cf. Iversen, 1971). Release of NE after electrical stimulation of the LC is only measurable in the presence of an uptake inhibitor (Tanaka *et al.*, 1976), so central NE is taken up quickly and efficiently. Moreover, central NE terminals appear to accumulate exogenous ^{3}H-NE (Descarries *et al.*, 1977).

2.4.3. *Enzymatical inactivation*

Released central NE is enzymatically inactivated by monoamine oxidase (MAO), catechol-O-methyl transferase (COMT) and aldehyde reductase. These conversions are rapid, and the resulting metabolite is MHPG or its SO_4-conjugated form (Rutledge and Johanson, 1967; Schanberg *et al.*, 1968). Enzymatically active MAO and COMT are present in all the CNS regions investigated (Saavedra *et al.*, 1976b; Hirano *et al.*, 1978). In the brain immunoreactive COMT is demonstrated only on non-neuronal elements, such as ependymal and other glia cells, and the choroid plexus, but the presence of small quantities on neurons cannot be excluded (Kaplan *et al.*, 1979). COMT is regarded as preventing the free diffusion of active NE through the CNS. NE released after electrical stimulation of the LC is rapidly converted into MHPG (Korf *et al.*, 1973a; Crawley *et al.*, 1978, 1979a).

2.5. SPECIFIC RECEPTORS

In the CNS, several different CAs and their receptors are present; these receptors have a varying affinity for NE and for adrenoceptor agonists and antagonists. In binding studies the central adrenoceptors, which are a subpopulation of the CA receptors, are therefore difficult to characterize. The available data however indicate that the central NE binding sites ("adrenoceptors") are similar to the peripheral ones: α_1 and α_2, and β_1 and β_2 adrenoceptors have been described (Nahorski 1978; Bylund 1978; U'Prichard and Snyder 1979; Minneman *et al.*, 1979a, b; Dolphin *et al.*, 1979). With fluorescent probes α- and β-adrenoceptors have been described, and their overall localization was in agreement with the localization of the NE terminals (cf. Melamed *et al.*, 1977; Atlas and Melamed, 1978; Young and Kuhar, 1979), but evidence has been published that at least part of these data are based on artifacts (Barnes *et al.*, 1980; Correa *et al.*, 1980). The adrenoceptors are present on LC cells, LC terminals and LC target cells (Cedarbaum and Aghajanian, 1977; Berthelsen and Pettinger, 1977; and see below).

2.6. IDENTICAL EFFECTS (ALSO PHARMACOLOGICALLY IDENTICAL)

2.6.1. *Introduction*

The effects of activity of the LC cells or of release/application of NE on the LC target cells will be discussed in more detail, because some of the conclusions are relevant to the understanding of the actions of the LC and NE. The effects of electrical stimulation of

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Woodward *et al.*, 1979; 142. Horn and McAfee, 1979; 143. Satoh *et al.*, 1979; 144. Marshall and Engberg, 1979; 145. Champagnat *et al.*, 1979; 146. Sasa and Takaori, 1979; 147. Moises *et al.*, 1979; 148. Siggins *et al.*, 1979; 149. Reader *et al.*, 1979; 150. Stone and Taylor, 1979; 151. Korf and Sebens, 1979; 152. Herbst *et al.*, 1979; 153. Nathanson and Glaser, 1979; 154. Porsche and Stefanovich, 1979; 155. Wu and Phillis, 1979; 156. Akagawa and Tsukada, 1979; 157. Schaefer *et al.*, 1979; 158. Igarashi *et al.*, 1979; 159. Phillis and Wu, 1979; 160. Göthert *et al.*, 1979; 161. Sasa *et al.*, 1979; 162. Szabadi, 1979; 163. Ioseliani and Dzhamaspishvili, 1979; 164. Vorob'ev and Nesterova, 1979; 165. Moises and Woodward, 1980; 166. Olpe *et al.*, 1980; 167. White and Neuman, 1980; 168. Chikamori *et al.*, 1980; 169. Lin, 1980; 170. Herrling, 1980a; 171. Fung and Barnes, 1980; 172. Freedman and Marwala, 1980; 173. Baraban and Aghajanian, 1980; 174. Ewart, 1980; 175. Fuenmayor and Gonzalez-Vegas, 1980; 176. Waterhouse *et al.*, 1980; 177. Sasa *et al.*, 1980; 178. Herrling, 1980b; 179. Segal, 1980; 180. Rogawski and Aghajanian, 1980a; 181. Solano-Flores *et al.*, 1980; 182. Rogawski and Aghajanian, 1980b; 183. Rogawski and Aghajanian, 1980c; 184. Taylor and Stone, 1980.

the LC, and of iontophoresis of NE on LC target neurons will be mentioned extensively, while the effects on other elements (cerebral blood vessels, glia cells and the CSF) will be mentioned shortly.

2.6.2. *LC- and NE-induced effects on neurons*

If NE is a neurotransmitter of the LC, then electrical stimulation of the LC must have effects on the LC target neurons identical to the effects of iontophoresis of NE. This is clearly the case (Table 1). It has to be admitted that strict electrophysiological tests have never been used to make certain that the target cell is directly (i.e. via adrenoceptors on the neuron from which the recording is made) influenced by the LC. Yet these effects are assumed to be evoked directly, because: (1) the regions investigated are LC target regions, (2) NE synapses and terminals have been identified in these regions (cf. Van Dongen, 1980), and (3) most authors agree on the effects of the LC. The response type described below is considered to be the typical LC/NE-induced response.

2.6.3. *Hyperpolarization and suppression*

NE hyperpolarizes its target neurons; depolarizations have only been described in one study (Fung and Barnes 1980) with intracellular recording (Tables 1 and 2). Concomitant with these hyperpolarizations, the "maintained activity" of the target cells was suppressed. (For reasons to be discussed below, care should be taken in using the words "exitation" (or "facilitation"), "inhibition", "activation" and "suppression"; in this paper, "activation" and "suppression" will be used in the meanings "increase" and respectively "decrease in the firing rate in the maintained activity", i.e. only as a description of an effect without implications for its mechanism, cf. Van Gisbergen *et al.*, 1974.) Electrical stimulation of the LC causes suppression with a long latency (30 msec, nucleus spinalis nervi trigemini, Sasa and Takaori, 1973; 40–70 msec, hippocampus, Finch *et al.*, 1978) and a long duration (typical 120 msec, Sasa and Takaori, 1973; Oishi *et al.*, 1977; Daugherty *et al.*, 1977; Finch *et al.*, 1978b; Igarashi *et al.*, 1979a; Aston-Jones, 1980); after prolonged stimulation (for instance 10 sec at 10 pulses/sec) the LC-induced hyperpolarizations and suppression can last as long as 60 sec (Hoffer *et al.*, 1973; Segal and Bloom, 1974a; Siggins *et al.*, 1976; Sinnamon *et al.*, 1978; Takemoto *et al.*, 1978). Since in awake animals the firing rate of the LC cells is about 10 spikes/sec (Hobson *et al.*, 1975; Foote *et al.*, 1980; Sakai and Jouvet, 1980), the LC causes a tonic suppression of the "maintained activity" of its target cells during such periods. During the LC/NE-induced hyperpolarization, the resistance of the membrane to transmembrane ion currents is increased (Table 2). An increase in the membrane resistance must be effected by closure of the ion channel with the smallest resistance, i.e. a closure of the K^+ channels.

2.6.4. *LC/NE-induced activations?*

A relatively small number of authors report the occurrence of NE-induced activations (Table 2, Szabadi 1979; Rogawski and Aghajanian 1980a, b, c; Fung and Barnes, 1980). These may either be evoked via an interneuron, be due to NE-induced vasoconstriction of cerebral blood vessels (Stone, 1971), or be the effect of interaction of NE with receptors for DA, octopamine or other compounds (cf. Hicks and McLennan, 1978, Bevan *et al.*, 1978a, b), but they could also be NE-induced activations evoked via receptors for which NE is the endogenous ligand (adrenoceptors) located on the neuron from which the recording is made (possibly α-adrenoceptors, Bevan *et al.*, 1977; Szabadi, 1979; Rogawski and Aghajanian 1980a, b, c; Fung and Barnes, 1980).

2.6.5. *Receptors involved*

In studies where the effects of electrical stimulation of the LC and iontophoresis of NE on the same neuron have been investigated, most LC/NE-induced effects came about via β-adrenoceptors, blocked by sotalol, propranolol and fluphenazine (Tables 1 and 2).

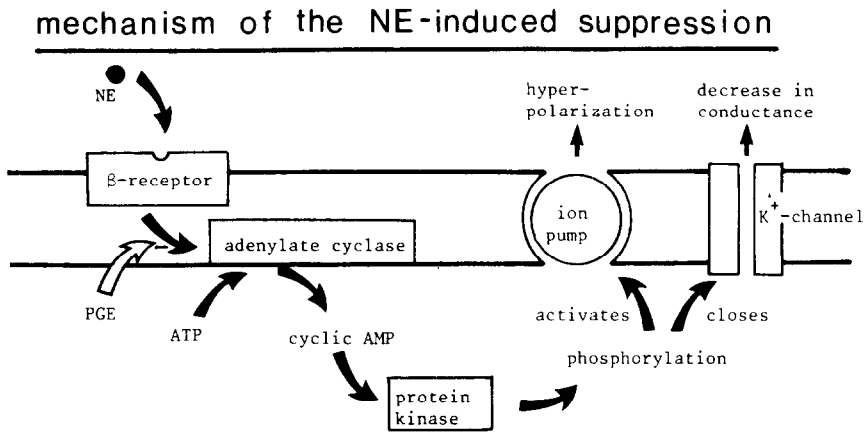

FIG. 1 Hypothetical mechanism of NE-induced suppression, hyperpolarization and decrease in membrane conductance; this mechanism seems to be the most plausible explanation of the NE effects on neurons as presented in the literature.

therefore a β-adrenoceptor is indicated in the figure on the mechanism of the NE-induced suppression (Fig. 1). The only well documented example of LC/NE-induced suppression via α-adrenoceptors is the NE-induced lateral suppression of the LC cells (Cederbaum and Aghajanian, 1976, 1977, 1978; Aghajanian *et al.*, 1977); and the only well documented example of NE-induced activations via α-adrenoceptors is the NE-induced activation of relay cells of the lateral geniculate nucleus (Rogawski and Aghajanian, 1980a, c). In a number of studies, effects of central NE via α-adrenoceptors on other organs or on behavior have been reported (sleep: Putkonen *et al.*, 1977; eating: Leibowitz *et al.*, 1978; endocrine: Weiner and Ganong, 1978; spinal reflexes: Kuraishi *et al.*, 1979; startle response: Davis *et al.*, 1979; conditioned avoidance: Hawkins and Monti, 1979). At the moment it is not at all clear whether these effects are due to interactions of adrenoceptor agonists and antagonists with adrenoceptors, or with receptors for which DA, octopamine or E is the endogenous ligand, and whether these receptors are located on neuronal cell bodies, on terminals or on other CNS target elements (blood vessels, glia cells).

2.6.6. *NE and cyclic AMP*

It is now generally accepted that NE causes its suppression through an increase in the adenylate cyclase activity, the enzyme that produces cyclic AMP (Korf and Sebens, 1979, reviews Iversen, 1977a, Nathanson, 1977). Both NE and cyclic AMP cause hyperpolarization with an increase in the membrane resistance (Siggins *et al.*, 1971a; Nathanson, 1977). Adenylate cyclase inhibitors diminish LC- and NE-induced responses (Segal, 1974; Nathanson *et al.*, 1976, 1977; Taylor *et al.*, 1978; Reches, 1978; Siggins *et al.*, 1979; Ebstein *et al.*, 1980), while on the other hand, inhibitors of phosphodiesterase (the enzyme that inactivates cyclic AMP) increase the LC-, NE- and cyclic AMP-induced responses (Siggins *et al.*, 1971b; Hoffer *et al.*, 1971b, 1973; Segal and Bloom, 1974a, b; Gähwiler, 1976). Since the response of cerebellar Purkinje cells to NE applied iontophoretically is much slower than to cyclic AMP (or GABA) ejected from the same electrode (Siggins *et al.*, 1971b; Hoffer, 1971b; Gähwiler, 1976), a slow process must be present between the release of NE and the synthesis of cyclic AMP. Not only electrophysiologically, but also biochemically, the effects of electrical stimulation of the LC, and of application of exogenous NE on the production of cyclic AMP are identical (Korf *et al.*, 1979). The activation of adenylate cyclase is not a unique property of NE; DA and some other neurohumors also activate adenylate cyclase (Nathanson, 1977).

2.6.7. *NE and prostaglandins*

The prostaglandins of the E series (PGE_1, PGE_2) diminish the effects of the LC's activity or of iontophoresis of NE on the LC target cells (Hoffer *et al.*, 1973; Segal and

TABLE 2. SURVEY OF THE LITERATURE. EFFECTS OF ELECTRICAL STIMULATION OF THE LC OR OF IONTOPHORETIC APPLICATION OF NE ON SINGLE UNIT ACTIVITY IN LC TARGET REGIONS, AND THE MECHANISM OF THESE EFFECTS (SEE KEY TO TABLE FOR THE ARTICLES THESE NUMBERS REFER TO).

	Whole brain	Spinal cord	Brain stem	Cerebellum	Telencephalic nuclei	Hippo-campus, g. pyriformis g. cinguli	Neocortex
Molecular level:							
Receptors:							
α- and β-adrenoceptors	97, 98, 162		20[Δ]	0			15, 34, 94[δ], 104, 125[δ], 126[δ], 129, 137
mainly α-adrenoceptors	132	4	62, 81[ψ], 95, 102[ψ], 103[ψ], 140[ψ], 173¶, 180	0	0	0	59, 126
mainly β-adrenoceptors	91, 130, 152, 153	0	8, 63, 146	135, 147, 172	127	47, 115	40, 54, 55, 76, 80, 82, 90, 96, 123, 134, 166
Cyclic AMP:							
involved	74, 75, 91, 97, 98, 99, 130, 131, 132, 133, 141, 152, 153, 157, 159	—	38, 135	24, 25, 27, 29, 39, 65, 66, 79, 88, 108, 135, 148	—	47, 49	76, 77, 80, 82, 91, 128, 129, 134, 135, 151
not involved	0	—	0	28, 33, 45	—	0	0
Prostaglandines involved	138	—	38	25, 27, 39		47, 49	—
Na,K-ATPase involved	50, 100, 154, 155, 156	—	—	78	—		50, 51, 52, 59, 60, 121, 122, 137
Calcium-ions involved	51, 99, 142, 160	—	—	27	—		50, 51, 52, 53, 60
Cellular level:							
Effects on the membrane (intracell.)							
transmembrane potential:							
depolarization	0	106†, 171	—	0	—	0	—
hyperpolarization	83, 141	11, 17, 18, 36, 61, 144		24, 39		170, 178, 179	—
membrane resistance:							
increase	83, 141	17, 18, 36, 106†, 144		24, 39		170, 178	
decrease	0	0		0		179	—

"Maintained activity"							
activation and suppression	162¶	—	62[c], 67*, 68*, 92*, 169	8[f]	0	—	13, 35, 54, 94[δ], 104, 125[δ], 126[δ]
mainly activation	0	—	8, 19, 20, 46, 95, 173¶, 180, 182, 183	0	0	—	14, 15, 16, 55, 95
mainly suppression	141	1, 2, 3, 4, 7, 84, 143	5, 10, 21, 22, 23, 30, 38, 81, 101, 102, 103, 111, 113, 140, 145, 161, 177	25, 26, 27, 28, 33, 39, 45, 64, 65, 66, 78, 79, 87, 88, 89, 107, 108, 141, 148, 172, 175	112, 181	6, 47, 48, 49, 71, 72, 73, 69, 114, 115	9, 31, 34, 40, 41, 50, 51, 52, 53, 58, 69, 70, 96, 116, 117, 118, 119, 120, 123, 149, 166, 174, 176, 184
Regional level:							
Response to neuroactive substances:		167	161	147§, 165§			176
increase in response	—	0	183				184
decrease in response	—	1, 3, 4, 7, 139	10			6, 49	31, 34, 41, 52, 53, 120, 124, 149, 174
Electrical and sensory stimulation:				64[o], 86[o], 141[o], 147[o]			
increase in response	0	167, 171	10, 180, 182, 183		0	0	0
decrease in response	141	1, 105[π], 139[π], 143	37, 42, 43, 56, 63, 85, 109, 146, 158, 168, 177[/]		93	6	31, 58, 124
Increase in "signal-to-noise ratio"	141			64, 86, 141, 147, 165		72	58, 141, 176

¶ Activation via α-adrenoceptors.
† Effect of intracellular injection of NE.
[π] Nociceptive responses suppressed; non-nociceptive responses not affected.
[λ] Receptors different from peripheral adrenoceptors.
[ψ] Effect of iontophoresis of NE on LC cells.
*Recording from *n. raphe dorsalis* cells, which are not adrenoceptive.
[/] Probably via interneurons.
[c] Depending on the location of the neuron.
[f] Depending on the location of the neuron.
§ Depending on the compound.
[o] Depending on the elements stimulated.
[δ] α-adrenoceptors: activation; β-adrenoceptors: suppression.
0 Investigated but not found.
— Not investigated.

Bloom, 1974a, b), but not the effects of cyclic AMP (Siggins *et al.*, 1971b; Hoffer *et al.*, 1971b). It has been suggested that the PGEs reduce the NE-induced increase in the adenylate cyclase activity (Hoffer *et al.*, 1971b; Nathanson, 1977). It is remarkable that the effect of prostaglandins on the NE-induced suppression is opposite to their action on the DA-induced effects (Nathanson, 1977).

2.6.8. *NE and Na,K-ATPase*

Ample evidence has been presented that NE increases the activity of the ouabain-sensitive Na,K-ATPase (the so-called Na,K-ATPase) and of the ouabain-insensitive Na,K-ATPase (the so-called Ca,MG-ATPase). The Na,K-ATPase has attracted special interest, since "the Na,K-ATPase is thought the enzymatic representation of the transmembrane Na-K-pump, which could have electrogenic properties under some conditions" (Ewart and Logan, 1978b). Since the NE-induced suppression of cerebellar Purkinje cells and somatosensory cortical cells is diminished by inhibitors of Na,K-ATPase (Phillis *et al.*, 1974; Yarbrough, 1976; review, Phillis, 1976) NE causes the suppression of its target cells through an increase in the Na,K-ATPase activity. This action of NE on an electrogenic Na,K-ATPase can explain the NE-induced hyperpolarization. Moreover, such an action can explain the difficulties in finding a reversal potential for the NE-induced effects (Marshall and Engberg, 1979). It is remarkable that no increase in the activity of the Na,K-ATPase by cyclic AMP has been found (Phillis, 1976; Akagawa and Tsukada, 1979). The activity of the Na,K-ATPase is increased not only by NE, but also by DA, while ACh, Glu or GABA have no effect on the Na,K-ATPase activity (Yarbrough, 1976; Desaiah and Ho, 1977; Akagawa and Tsukada, 1979; Schaefer *et al.*, 1979).

2.6.9. *NE and calcium ions*

The NE-induced suppression of somatosensory cortical cells is reduced by compounds interfering with Ca^{2+} transport and binding (Phillis *et al.*, 1974; reviews, Phillis, 1974, 1976). The action of Ca^{2+} could be due to interactions of Ca^{2+} with adenylate cyclase and/or phosphodiesterase (Ahn *et al.*, 1976; Nathanson *et al.*, 1976; review, Rasmussen and Goodman, 1977), or to a change in membrane properties either due to binding of Ca^{2+} to the membrane, or due to fluxes of Ca^{2+} through it (Phillis, 1974, 1976; see also Orrego, 1979).

2.6.10. *A hypothetical mechanism of the NE-induced suppression*

The data on the mechanism of the NE-induced suppression are summarized in Fig. 1. NE causes a two-fold action: (1) an increase in the activity of an electrogenic ion pump which causes an outward current of Na^+ (or perhaps K^+ or Ca^{2+}), and consequently a hyperpolarization (Phillis 1974), and (2) a closure of K^+ channels which is reflected as an increase in the membrane resistance (cf. Phillis, 1976; Marshall and Engberg, 1979). In this process, cyclic AMP, prostaglandins, Na,K-ATPase and Ca^{2+} are involved. It has to be admitted that no interpretation of the mechanism of NE action on the target cell membrane has ever been presented in the literature that is consistent with all the findings mentioned above, and this drawback applies to my interpretation too (Fig. 1). (Points of agreement that NE *and* cyclic AMP cause hyperpolarization with an increase in the membrane resistance, and that NE *does* cause an ouabainsensitive suppression, while an inconsistent point is that cyclic AMP has been reported as *not* influencing the Na,K-ATPase activity in the CNS. I cannot however think of a simple interpretation that is in agreement with all data.)

2.6.11. *Actions of NE on non-neuronal elements in the CNS*

NE terminals on other CNS elements than neurons have been described (Section 2.1.), but their action is much less investigated than the action of NE terminals on neurons. Conflicting data have been published on the effects of activity of the LC on the cerebral blood flow (review, Van Dongen, 1980, pp 61–63). My interpretation of the data found in

the literature is that activity of the LC cells causes an increase in the cerebral blood flow and in the cerebral metabolism in the LC target regions (cf. Edvinsson, 1975; Edvinsson *et al.*, 1979; Harik *et al.*, 1979; Cummins and Keller, 1979; but see also Schwartz *et al.*, 1978; Abraham, 1979). NE causes phosphorylation and an activation of carbonic anhydrase in glia cells of the cerebral cortex (Church *et al.*, 1980). The effects of NE reaching the ventricle are unclear. Intracerebroventricular injections of NE and adrenoceptor agonists or antagonists have yielded inconsistent results (cf. Ramm, 1979), and it is even unclear whether endogenous NE just leaked away into the CSF having no action of its own and being rapidly degraded, or whether it interacts with adrenoceptors influencing someway the cerebral information processing.

2.7. CONCLUSIONS

2.7.1. *NE as a neurotransmitter of the LC*

Taking together the above mentioned data on LC terminals and the effects of NE released from the LC terminals, the above mentioned criteria for "neurotransmitters" and so on, and using the criteria not too conservatively, my conclusion is: *NE is a synaptic and a nonsynaptic neurotransmitter of the LC cells, and NE released from LC terminals into the ventricle might be a CSF neurohormone.* What then are the similarities and differences between the effects of synaptic and nonsynaptic released NE? The above mentioned effects of electrical stimulation of the LC probably come about through synaptic and nonsynaptic terminals and thus reflect the similarities between them. Some speculative remarks can be made on the differences. A synaptic release of NE assures strictly local effects with a fixed, relatively short latency on fixed target elements, while freely released NE may have more distant effects with a longer, variable latency on variable target elements. Distant effects of freely released NE, however, are probably still restricted, because (1) freely released NE will be rapidly degraded and inactivated by MAO and COMT, which are present throughout the CNS, and (2) the distribution of central adrenoceptors is similar, but not identical, to the distribution of the central NE terminals (Palacios and Kuhar, 1980). NE reaching the ventricle by direct release or diffusion (cf. Ziegler *et al.*, 1976; Perlow *et al.*, 1978; Adèr *et al.*, 1979b) may have distant effects, if it has any.

3. Interaction of NE from the LC with other Neurohumors, and its Effect on CNS Signal Processing

3.1. INCREASE IN THE SIGNAL-TO-NOISE RATIO?

The "maintained activity" of cerebellar Purkinje cells is suppressed by NE from the LC, while the activations and suppressions of the activity of the same cell evoked by electrical stimulation of the climbing fibers, the parallel fibers, the motor cortex, the limbs or the vibrissae were increased or left unaffected by NE—and in case that the latter activations or suppressions were decreased, this decrease was smaller than the decrease in the "maintained activity"—(Freedman *et al.*, 1976, 1977; Woodward *et al.*, 1979). The "maintained activity" of neurons in the auditory and somatosensory cortex is similarly suppressed by NE from the LC, while also in these regions both the activations and the suppressions to species-specific vocalizations and to tactile stimuli remained intact, or were even enhanced (Foote *et al.*, 1975; Woodward *et al.*, 1979; Waterhouse *et al.*, 1980). The "maintained activity" was considered to be noise, and the experimenter-induced activity was regarded as signal, so the signal-to-noise ratio of these cerebellar and neocortical neurons was said to be increased (see below for objections to this view, and for a less prejudiced description). In the visual cortex, the duration and depth of the recovery cycles after visual stimulation were reduced by NE from the LC (Vorob'ev and

Nesterova, 1979), which also indicated a NE-induced improvement in the cortical signal processing. Similarly, in the hippocampus, the LC has been reported as selectively enhancing the response to a (initial neutral) stimulus which was coupled to a significant stimulus (e.g. food; Segal and Bloom, 1976b); this was also regarded as a LC-induced increase in the signal-to-noise ratio. On the other hand, both the "maintained activity" and the activations of dorsal lateral geniculate nucleus neurons due to electrical stimulation of the optic tract, were increased by iontophoresis of NE and by electrical stimulation of the LC (Rogawski and Aghajanian, 1980a, b, c); the implications of these findings will be mentioned below. A selective reduction of the "maintained activity" compared to the investigator-induced activity is not a unique property of NE; GABA has a similar action in the cerebellum and the neocortex, although by means of a different membrane mechanism (Foote *et al.*, 1975; Freedman, 1977; Waterhouse and Woodward, 1980).

3.2. Interaction of NE with other Putative Neurotransmitters

Recently, data have been presented that the actions of NE can be best understood by its interaction with various putative neurotransmitters: this might explain NE's effects both on stimulation-induced activity and on the so-called maintained activity (see below). The GABA-induced suppression of cerebellar Purkinje cells and of parietal and somatosensory cortical cells is enhanced by NE (Moises *et al.*, 1979; Moises and Woodward, 1980; Waterhouse *et al.*, 1980; Taylor and Stone, 1980), while at the same time the Gly-induced suppression of these cells was diminished. The ACh- and Glu-induced activation of cerebellar Purkinje cells, dorsal lateral geniculate nucleus relay cells and somatosensory cortical cells is reported as being enhanced by NE (Moises *et al.*, 1979; Moises and Woodward, 1980; Waterhouse *et al.*, 1980; Rogawski and Aghajanian, 1980c). Some papers indicated a NE-induced reduction of the ACh- and Glu-induced activations but this may be due to relatively large NE currents (Legge *et al.*, 1966; Frederickson *et al.*, 1971; Segal, 1974; Phillis and Limacher, 1974; Ewart and Logan, 1978a; Reader, 1979a). The adenosine-induced suppression of parietal cortical cells is enhanced by NE (Taylor and Stone, 1980). It is likely that in the future further examples will be described where the combined action of 2 putative neurotransmitters on one target cell is not simply the combination of their separate actions at the cellular level, but a more complicated interaction. If the action of the putative neurotransmitters at the molecular level (see Van Dongen 1980 for "levels") is known, their simultaneous action can be understood both at the molecular and at the cellular level.

4. Implications of these Findings

4.1. LC/NE-induced Suppression is not Inhibition

The prototype of "classical inhibition" is the inhibition of spinal α-motoneurons by Renshaw cells; the transmitter involved is most probably Gly, but it could also be either taurine or β-analine (cf. Sonnhof *et al.*, 1975; Curtis and Johnson, 1976; Davidson, 1976; Nicoll *et al.*, 1976). The mechanism of the Renshaw-induced inhibition is opening of K^+ channels (Fig. 2; Curtis and Johnson, 1976; Davidson, 1976). The NE-induced suppression involves a different mechanism (Figs. 1 and 2). The most striking difference between Gly-induced inhibition and NE-induced suppression at the molecular level is that the Gly-induced inhibition is a passive process, the opening of K^+ channels, while the NE-induced suppression is an active, energy requiring process, which involves the degradation of ATP for the synthesis of cyclic AMP and for actively pumping ions across the membrane. The most striking difference at the cellular level is that Gly causes a similar suppression of the "maintained" and experimenter-induced activity, while NE influences the various transmitter-induced activities in different ways.

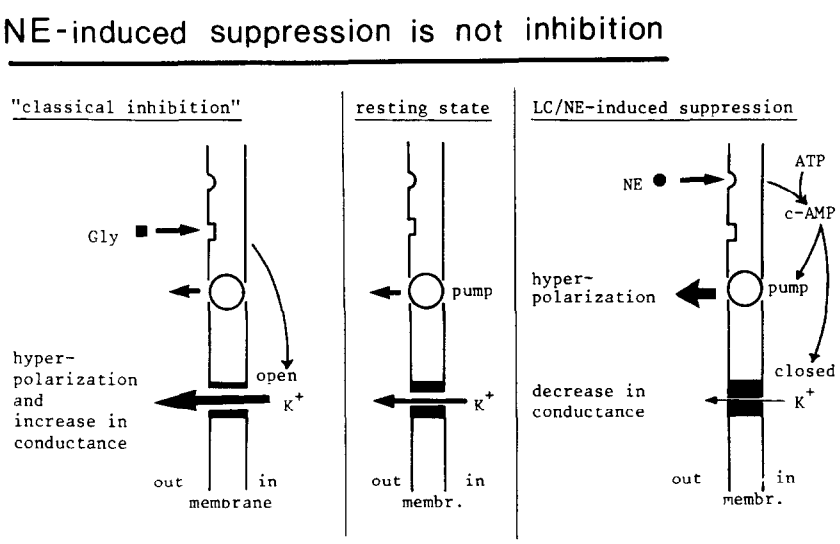

FIG. 2 Diagram illustrating the differences between "classical inhibition" (as induced by glycine) and the LC/NE-induced suppression.

4.2. NE AND THE "MAINTAINED ACTIVITY" OF ITS TARGET NEURONS

The "maintained activity" of the LC's target neurons might be an effect of 2 causes.

1. The transmembrane potential of neurons without active afferents is not fixed, but shows fluctuations ("membrane noise"). One can imagine that the threshold for spike generation is occasionally reached by such stochastic fluctuations; this would result in a "spontaneous activity" of this neuron, which is propagated further in the CNS.

2. A number of neurons give off activating pulses to a neuron, inducing a "maintained activity" in the latter neuron; the membrane noise of this neuron causes a stochastic transmission of these afferent activating pulses.

Activity of the LC cells causes release of NE, which has a dual effect.

1. NE activates an electrogenic ion pump causing hyperpolarization of its target neurons; this effect diminishes the probability of firing by chance: the "spontaneous activity" is suppressed.

2. NE closes K^+ channels of its target neurons, thereby increasing the membrane resistance. The effect of NE on actions of other neurohumors depends on the molecular mechanism of the latter's effect. Suppose that we are dealing with a "classical excitatory" neurotransmitter, the molecular mechanism of whose action is opening of Na^+ channels, resulting in depolarization. The action of such neurotransmitter on the cellular activity will be increased by NE, because an identical outward Na^+ current (or even a greater Na^+ current due to a greater electrical force on Na^+ during hyperpolarization) causes a larger depolarization, when the membrane resistance is increased (cf. Weight, 1974; and in Dismukes, 1979).

One must expect that the effect of activity of the LC, or of iontophoresis of NE, on the "maintained activity" of its target cells depends on the main afferent influence. A tonically Glu-driven neuron will be activated (cf. Rogawski and Aghajanian, 1980c), while a tonically GABA-driven neuron may be expected to be suppressed.

4.3. THE PRINCIPLE OF NEUROCHEMICALLY SPECIFIC EFFECTS

NE appears to have unique effects on its target neurons, and it is probable that other putative neurotransmitters each have differing unique effects on their target neurons (Bonkowski and Dryden, 1977). Therefore, "the important and universally accepted point: different presynaptic fibers can exert one of two fundamentally opposite effects on postsynaptic neurons, either facilitation or inhibition" (Patton, 1965, p 168) is not valid

any more: various terminals can exert one of more than two different effects. The effect of a neurotransmitter is adequately characterized at the molecular level, i.e. by its effects on the different ion channels, pumps and other molecules. Such effects not only depend on the neurotransmitter involved, but also on its receptors (e.g. ACh, Purves 1976; and DA, Kebabian and Calne 1979; Cools and Van Rossum, 1980). (For this reason I did not speak about the "Principle of Neurotransmitter Specific Effects", but about the "Principle of Neurochemically Specific Effects". Some similarities and differences between the neurochemical effects of NE and other neurohumors have been mentioned above.) When the Neurochemically Specific Effects of two neurotransmitters are known, their simultaneous effect can be understood.

4.4. NEUROMODULATION?

It is fashionable to describe the effect of NE (and of other neurotransmitters) in terms of "neuromodulation" (or "to modulate", "neuromodulatory", "neuromodulator", cf. Dismukes and commentaries 1979). Three meanings of these words will be discussed shortly. Some authors use these words in their common sense meaning, and not in more-or-less strictly defined meanings. A common sense meaning is the following (cf. Lembeck in Dismukes, 1979): "*M* modulates the effect of *B*" means "*M* influences the effect of *B*". In this case, the word "to influence" is sufficient, and "to modulate" is superfluous and is unjustly suggested to be a technical term.

4.5. MODULATION VERSUS EXCITATION AND INHIBITION

An effect of a neurotransmitter is called "modulation" by some authors, when this effect is not "simply excitation or inhibition" (Dismukes 1979; Libet in Dismukes, 1979). This would be nice, when we knew what "excitation" and "inhibition" exactly is, or when at least these words were conventionally, but strictly defined. A tentative description of "excitation" could be "opening of Na^+ channels leading to depolarization" (such as the effect of ACh via nicotine receptors, and the effects of L-Glu and L-Asp); and a tentative description of "inhibition" an "opening of K^+ channels leading to hyperpolarization" (such as the effect of the presumably glycinergic Renshaw cells). (It remains however questionable whether all effects one wants to call "excitation" or "inhibition" come about via these mechanisms.) Note that "excitation" and "inhibition" are hereby reformulated as Neurochemically Specific Effects. Another tentative description of "inhibition" at a higher (cellular) level is a similar decrease in both the maintained and the experimenter-induced activity of a neuron. Consequently the effects of NE both at the molecular and at the cellular level are not simply "inhibition".

4.6. DOES NE HAVE EFFECTS OF ITS OWN?

According to a number of authors, a compound has a "neuromodulatory effect", when it has no effect of its own but only influences ("modulates") the effects of other neurotransmitters (cf. Torda 1977; Rogawski and Aghajanian, 1980c; Butcher, Evans, Iversen, Kupferman and Libet in Dismukes, 1979): a neuromodulator would not influence the membrane potential nor the maintained firing rate. NE seems to have effects of its own—activation of an electrogenic ion pump and closure of K^+ channels—and only in one study (Sasa *et al.*, 1979) some indications have been published that these effects would come about via other neurotransmitters. This applies to the NE-induced effects via β-adrenoceptors (see above). It is uncertain whether the effects of NE via α-adrenoceptors only come about via other neurotransmitters (such as Glu in the dorsal lateral geniculate nucleus), or also include effects of NE of its own; investigations with intracellular recording can solve such problems (cf. Rogawski and Aghajanian, 1980c).

4.7. CONCLUSIONS ON THE EFFECTS OF NEUROHUMORS

An implicit assumption in the use of the word "neuromodulator" (or derived words) is

that compounds can be distinguished (the "neurotransmitters") that transmit the "really relevant" neural messages (the "signals", the "excitations" and "inhibitions" in the CNS), and that other compounds (often called "neuromodulators") only modify these messages. It would imply that we already know what the signals are (i.e. the activity to be modulated), what the modulating activity, and what the irrelevant activity ("noise") is. Such a view leads to confusing questions: for instance, both NE and GABA are said to increase the signal-to-noise ratio of cerebellar and neocortical cells (Foote *et al.*, 1975; Freedman *et al.*, 1977; Taylor and Stone, 1980); does then NE modulate the GABA-induced effects, or does GABA modulate the NE-induced effects, or—and this is my opinion—are such questions irrelevant? The dichotomy "neurotransmitter" versus "neuromodulator" and the dichotomy "excitation" versus "inhibition" are in my opinion an inadequate and too simple description of the various effects of neurohumors: I prefer the analysis of effects of neurohumors in terms of Neurochemically Specific Effects to a discussion on definitions in the classification of neurohumors (cf. Dismukes, 1979; especially the words "neuromodulation" and "neuromodulator" have created much confusion; I would recommend to avoid them altogether). Moreover, I prefer a less prejudiced view on neural activity: each neural activity is both a representation of something else (i.e. it has a "meaning"), *and* has effects which are finally, and often indirectly, effects on behavior (see Van Dongen, 1980, pp. 217–266). So I prefer the analysis (1) of the Neurochemically Specific Effects of the different neurohumors (as has been done in this paper for NE of the LC), and (2) of the effects of neural messages at the different levels, from molecular (Neurochemically Specific Effects) to behavioral effects (as has been attempted for the LC in Van Dongen, 1980).

5. Summary

1. The present paper reviews the data relating to the central noradrenergic (NE) transmission of the locus coeruleus (LC). According to the conventional criteria for neurotransmitters, NE can be regarded as a synaptic and nonsynaptic neurotransmitter of the LC and possibly as a neurohormone which acts after transport via the cerebrospinal fluid.

2. The most often described response to iontophoresis of NE, and to electrical stimulation of the LC is a reduction in the maintained firing rate via β-adrenoceptors, concomittant with hyperpolarization and with an increase in the membrane resistance. It is suggested that these effects come about by an increase in the activity of an electrogenic ion pump and by a closure of K^+-channels. The molecular mechanism of this action of NE might explain the interaction of NE with other putative neurotransmitters. The response of LC-target neurons to other stimuli remains relatively intact during a NE-induced reduction of the maintained firing rate: the "signal-to-noise ratio" of LC-target cells is regarded by many authors as being increased by NE. In this paper, it is suggested that LC's actions can be better understood by the interaction of NE with other putative neurotransmitters, than as an increase in the signal-to-noise ratio: NE increases the response to some putative neurotransmitters, and decreases the response to others. The conclusion that NE from the LC improves the signal processing in its target regions seems attractive, but cannot yet be shown to be false or true.

3. Iontophoresis of NE and electrical stimulation of the LC have been reported as increasing the maintained firing rate of a minority of neurons via α-adrenoceptors. The cellular and molecular mechanism of this action is scarcely investigated.

4. It is suggested that the action of a putative neurotransmitter is complex, such that the dichotomy "excitation" versus "inhibition" is a description that is inadequate to describe the various neurotransmitters' effects: the effects of neurotransmitters can be described adequately as "neurochemically specific effects".

5. The words "neuromodulation" and "neuromodulator" appear to be used with a variety of meanings, which makes them meaningless; it is recommended not to use them at all.

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