8

Amine Neurotransmitter Actions in the Hippocampus

HELMUT L. HAAS

Neurochirurgische Universitätsklinik,
Zurich, Switzerland

I. Introduction

Afferent fibers to the hippocampus contain the amine transmitter candidates acetylcholine (ACh), histamine (HA), noradrenaline (NA), serotonin (5-HT) and dopamine (DA) (Storm-Mathisen, 1977a,b). These substances are probably released from synaptic and non-synaptic varicosities or endings on hippocampal neurons and a great variety exists in the location and characteristics of their release, action, inactivation and metabolism. None of these amines seems to be involved directly in the "classical" transmission of signals to (and from) the principal neurons (pyramidal and dentate granule cells, see Andersen, 1975) but there is good evidence that they modulate various aspects of the rapid information transfer in the hippocampus. The term transmitters is used here in a broad sense implying only that they are chemical mediators of information between nerve cells. It seems premature, considering the present state of our knowledge of amine actions, to introduce a more specific nomenclature. Apart from ACh, the amines may only have a very restricted role in the concert of transmitter actions, and the attention paid in particular to those amines which can be visualized by histochemical methods may be quite disproportionate to their functional importance. Thus, the catecholamine-containing fibers entering the hippocampus have been estimated to represent less than 1 % of the total input (Storm-Mathisen, 1977a). In spite of this small quantity, stimulation of amine-containing fibers results in measurable effects and destruction of these inputs leads to specific changes in the hippocampus.

This paper describes and discusses amine actions at the single cell or membrane level in the hippocampus. Such studies have used extra-cellular recording and ionophoresis, and recently, through intracellular recording (mostly in hippocampal slices), more specific information has become available. The localization and input pathways of these putative transmitters have been well discussed by Storm-Mathisen (1977a,b).

II. Acetylcholine (ACh)

There is a large body of evidence from various tracing and lesioning experiments in several species for a cholinergic septo-hippocampal pathway probably projecting to the proximal dendritic regions of principal cells and to interneurons (Lewis *et al.*, 1967; Lynch *et al.*, 1972; Mellgren and Srebro, 1973; Mosko *et al.*, 1973; Segal and Landis, 1974; Storm-Mathisen, 1977a,b). Electrical stimulation of these fibers leads to ACh release (Smith, 1974; Dudar, 1975). A small number of intrinsic cholinergic neurons may also be present in the hippocampus (Storm–Mathisen, 1974).

A slow muscarinic excitatory action of ACh, first reported by Krnjević and Phillis (1963), has been analysed by several investigators on hippocampal pyramidal cells (Stefanis, 1964; Biscoe and Straughan, 1966; Steiner, 1968; Bland *et al.*, 1974; Bird and Aghajanian, 1976; Segal, 1978; Herrling, 1981). As was shown with cerebral cortical neurons (Krnjević *et al.*, 1971), depolarization by ACh is accompanied by an increase in membrane resistance, presumably a closure of potassium channels (Kelly *et al.*, 1979; Adams *et al.*, 1981; Benardo and Prince, 1981; Dodd *et al.*, 1981; Haas, 1982). This depolarization has a slow onset and a long duration, suggesting an intracellular effect outlasting the drug receptor interaction. This interpretation is supported by the observation that atropine blocks the actions of ACh and carbachol with a long latency of onset. Atropine itself produces changes in membrane properties opposite to those of the cholinergic drugs, possibly by antagonizing a tonically present action of ACh (Benardo and Prince, 1981; Haas, 1982). In cultured slices, Gähwiler and Dreifuss (1982) could block actions of ACh in high Mg^{2+}- or Co^{2+}-containing, but not in tetrodotoxin-containing, media and they suggest the presence of a depolarizing current mainly carried by Ca^{2+} ions. A contribution of Ca^{2+} and Na^{+} inward movements would also be expected from the finding of Benardo and Prince (1981) that ACh enhances anomalous rectification.

Furthermore, a presynaptic inhibitory action (Yamamoto and Kawai, 1967; Hounsgaard, 1978; Valentino and Dingledine, 1981; Gähwiler and Dreifuss, 1982) and a powerful disinhibitory effect (Krnjevic *et al.*, 1980; Valentino and Dingledine, 1981; Gähwiler and Dreifuss, 1982; Haas, 1982) of ACh were described in the rat hippocampus *in situ* and in slices. These effects are blocked by atropine but a nicotinic component may also be present (Bird and Aghajanian, 1976; Segal, 1978). The effect of carbachol, an acetylcholinesterase-resistant agonist, on CA1 pyramidal neurons in hippocampal slices of the rat is illustrated in Fig. 1.

Repetitive stimulation of afferent fibers leads to a failure of hippocampal inhibitory postsynaptic potentials (IPSPs) rather similar to the disinhibition caused by ACh (Krnjevic *et al.*, 1980). The stimulation-induced disinhibition

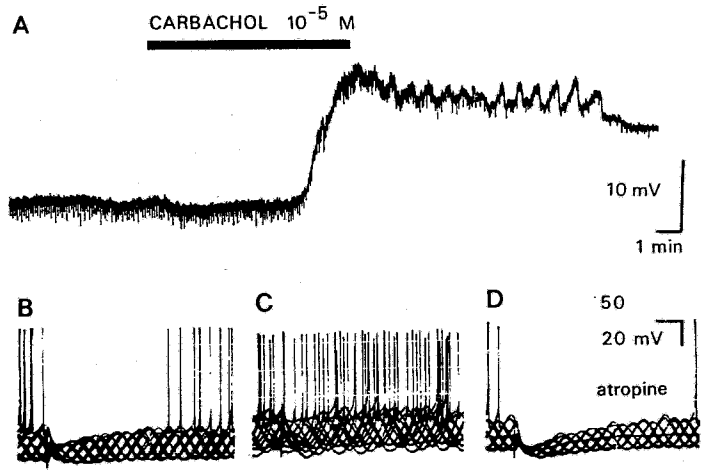

FIG. 1. Effect of carbachol perfusion on a CA1 pyramidal neuron in a rat hippocampal slice. (A) Membrane potential. Carbachol causes a long-lasting depolarization. (B, C, D) Intracellular injection of an alternating current of 10 Hz forms an envelope whose width is proportional to the membrane resistance at any time during the sweep. Ten sweeps are superimposed. Appropriate electrical stimulation of the stratum radiatum evokes an inhibitory postsynaptic potential (IPSP). B: control, C: during carbachol action, the wider envelope indicates a conductance decrease. The IPSP and the pause in action potential firing are virtually abolished. D: one hour after withdrawal of carbachol and addition of atropine (10^{-6}M) to the bath. The IPSP is now stronger than in B.

is however not blocked by atropine (10^{-6}M in slices, Haas, unpublished observations). Effects of non-cholinergic afferents to the hippocampus are potentiated in the presence of ACh (Alvarez-Leefmans and Gardner-Medwin, 1975; DeFrance *et al.*, 1977). Hippocampal neurons have been shown to become supersensitive to ionophoretically applied ACh but not to glutamate and GABA during kindling (a repeated stimulation program leading to seizures, Burchfiel *et al.*, 1979). The stimulation used by these authors must also have induced long term potentiation (LTP; Bliss and Lømo, 1973), which has in fact been suggested to participate in the generation of epileptic phenomena (Andersen, 1969). Inhibition *per se*, however, was found to be unchanged during LTP (Haas and Rose, 1981) and LTP could equally well be elicited in a medium containing atropine (Haas, unpublished observations).

In summary, ACh seems to cause a number of actions including direct excitation, disinhibition, and presynaptic inhibition on principal cells of the hippocampus. The afferents from the septum can thereby very effectively alter hippocampal activities.

III. Histamine

Studies of the specific histamine (HA) synthesizing enzyme histidinedecarboxylase (HD) after various lesions suggest that histaminergic fibers arise from the supramammillary region of the mesencephalon and project to the hippocampus through a dorsal and a ventral path (Garbarg *et al.*, 1974; Barbin *et al.*, 1976; Haas *et al.*, 1978). Horseradish-peroxidase injections into the hippocampus have traced such projections (Segal and Landis, 1974; Pasquier and Reinoso–Suarez, 1976) but a direct histochemical visualization of histaminergic fibers is not yet possible.

The firing of hippocampal pyramidal and dentate granule cells is depressed by ionophoretically applied HA and impromidine (an H_2-receptor agonist), and this depression is selectively antagonized by the H_2-receptor antagonists metiamide and cimetidine in urethane anesthetized rats (Haas and Wolf, 1977) and *in vitro* (Haas, 1981b). Fornix stimulation, which excites histaminergic and other fibers, causes a long lasting inhibition of hippocampal pyramids. The later portion of this inhibition is reduced by metiamide (Fig. 2; Haas and Wolf, 1977). This result supports the idea of an

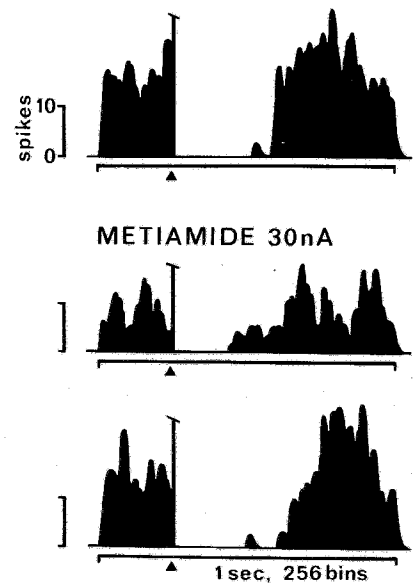

FIG. 2. Smoothed peristimulus time histogram (64 sweeps) from a hippocampal pyramidal cell in a urethane anaesthetized rat. In spite of a reduction in firing rate the pause in action potential firing after fornix stimulation (▲) is reduced during iontophoretic application of the histamine H_2-antagonist metiamide.

histaminergic afference to the hippocampus. Although these experiments clearly relate the depressant action of HA to the H_2-receptor, an H_1-receptor participation cannot be excluded. Both H_1- and H_2-receptor agonists stimulate cyclic AMP formation (Green *et al.*, 1978; Schwartz *et al.*, 1980) and H_1-receptors have a specific distribution in the hippocampus (Palacios *et al.*, 1981).

The depression of firing by HA is associated with a hyperpolarization and, possibly, with a moderate conductance increase of potassium ions (Haas, 1981a; Fig 3). Such hyperpolarizations are observed after HA administration from micropipettes to the surface of, or into, hippocampal slices by drops, pressure ejection and ionophoresis. With drop applications, cells are also often depolarized but in contrast to the hyperpolarizations this effect does not persist in low Ca^{2+}/high Mg^{2+} or in the presence of tetrodotoxin and is therefore presynaptic (Haas, 1981a; Haas and Geller, 1982). Segal (1980a, 1981a) has also described such effects together with an enhancement of excitatory postsynaptic potentials (EPSPs) in the CA1 and CA3 area. Although these findings may reflect the presence of HA receptors on interneurons or synaptic endings, they could equally well be explained by the depressant action of HA on neighboring pyramidal cells.

The sometimes undetectable change in membrane conductance might be explained by an effect remote from the soma. However, the possibility that

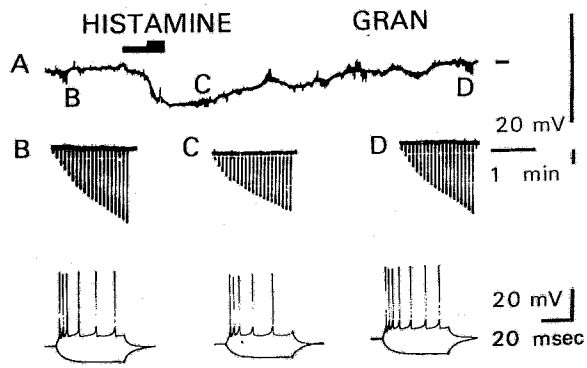

FIG. 3. Intracellular recording from a dentate granule cell in a hippocampal slice from the rat. (A) Membrane potential (68 mV). Histamine (10^{-4}M) was applied by pressure ejection from a micropipette into the slice during the time indicated by black bars above the trace (20–50 mm Hg). (B, C, D) Upper traces illustrate hyperpolarizing current pulses from 0.1 to 2.0 nA at the times indicated in A. Lower traces show ± 0.5 nA current injection at an extended time base. During histamine action there is a conductance increase and a reduction in excitability demonstrated by the smaller voltage responses to constant current injection and the reduced number of action potentials.

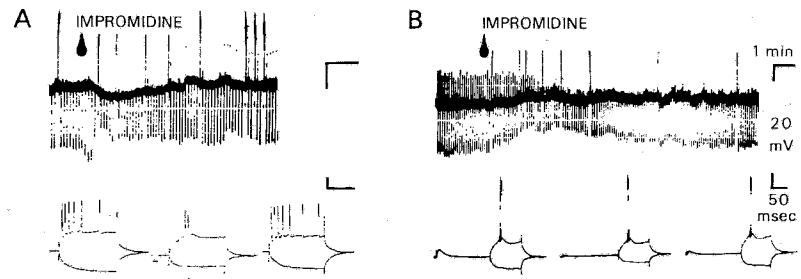

FIG. 4. Effects of impromidine, a histamine H_2-agonist, on dentate granule cells in hippocampal slices of the rat. Microdrop application (ca 10 nl, 5.10^{-5}M, at the drop symbols). (A) An hyperpolarization with a conductance increase, downward deflections are from constant current injection (-1 nA). Lower traces illustrate responses to ± 1 nA pulses before, during (middle), and after the impromidine action. Note the conductance increase and the reduced number of action potentials. (B) Impromidine causes a depolarization with a conductance increase in another cell. Lower traces are similar to (A) but also show an EPSP after perforant path stimulation. The EPSP is markedly reduced for a prolonged period.

HA activates an energy dependent process (Lee and Phillis, 1977; Sastry and Phillis, 1977) is still open. Hyperpolarizations by HA are smaller in highly polarized cells and reach voltage levels more negative than the chloride equilibrium potential (up to -90 mV); these more negative voltage levels also occur when chloride ions are injected into the cells in order to reverse the IPSP. This makes a significant role for chloride ion movements in the mechanism of HA action unlikely. The EPSP–IPSP sequence evoked by afferent fiber stimulation is sometimes reduced by HA, as one might expect during the shunting effect of an increased conductance. Similar actions of impromidine are illustrated in Fig. 4.

Taken together, these data indicate that HA hyperpolarizes CA1 pyramidal and dentate granule cells by an action on the postsynaptic membrane, possibly by a conductance increase of potassium ions in specific dendritic loci. The effect is associated with H_2-receptors. HA released from the fibers ascending in the medial forebrain bundle and entering the hippocampus and the area dentata through the fornix and perforant path could therefore exert a spatially and functionally specific modulation of rapid information transfer in these regions and provide a mechanism for midbrain and hypothalamic influences on hippocampal function.

IV. Noradrenaline

Catecholamine fluorescent fibers entering the hippocampus originate primarily in the nucleus coeruleus (Pickel *et al.*, 1974). Ionophoretically-applied

noradrenaline (NA) depresses the firing of hippocampal neurons (Herz and Nacimiento, 1965; Biscoe and Straughan, 1966). The detailed investigation by Segal and Bloom (1974a,b, 1976) shows that the depressant effects of both local application of NA and stimulation of locus coeruleus are antagonized by beta-blockers and enhanced by a NA uptake blocker. Neurons in rats treated with 6-hydroxydopamine become hypersensitive to NA but do not respond to locus coeruleus stimulation. Cyclic AMP mimicks the NA actions which are partially blocked by some prostaglandins (which modulate adenylate cyclase) and enhanced by papaverine (which blocks phosphodiesterase). The authors thus suggested that NA may act via the cyclic AMP system.

More recently, Langmoen *et al.* (1981) analysed the action of topically applied NA using intracellular recordings from hippocampal slices. They found an hyperpolarization associated with a conductance increase, possibly for chloride ions, which persists when the cells are synaptically isolated with low Ca^{2+}/high Mg^{2+} in the perfusion fluid. Interestingly, there is a much larger change in membrane responses to depolarizing than to hyperpolarizing current pulses, an effect which can be explained by a NA-induced decrease in anomalous rectification (Hotson *et al.*, 1979). The reduction of the response to depolarizing current is clearly apparent only after about 10 msec. (Fig. 5). This means probably a reduction in Ca^{2+} and Na^{+} inward movements. Since hyperpolarizations could not be obtained with NA in ouabain-treated slices and at low temperature (Segal, 1981b), NA seems to activate also a Na-K pump (Lee and Phillis, 1977; Sastry and Phillis, 1977; Heinemann *et al.*, 1978). With cyclic AMP, Segal *et al.* (1980, 1981b) obtained similar actions which were also blocked by ouabain. The effect of NA on EPSPs was found to be variable but IPSPs were always reduced (Langmoen *et al.*, 1981).

On dentate granule cells, in hippocampal slices from rats, I have also observed hyperpolarizations, moderate conductance increases, and a reduction in excitability. This is illustrated in Fig. 6.

In *in vivo* experiments on cats Herrling (1981) has applied NA from a compound electrode for intracellular recording and extracellular ionophoresis. He found a fast hyperpolarization which is accompanied by a marked increase of the apparent input resistance (conductance decrease) and a reduction in the size of EPSPs and action potentials. A similar change has been observed with NA application on spinal motorneurons (Marshall and Engberg, 1979) and on cerebellar Purkinje-cells (Siggins *et al.*, 1971).

Ionophoretically-applied lithium ions can antagonize the actions of NA and serotonin but not those of GABA and ACh in the hippocampus (Segal, 1974). Although this effect might be explained by the excitant action of lithium on many neurons in the central nervous system (Haas and Ryall,

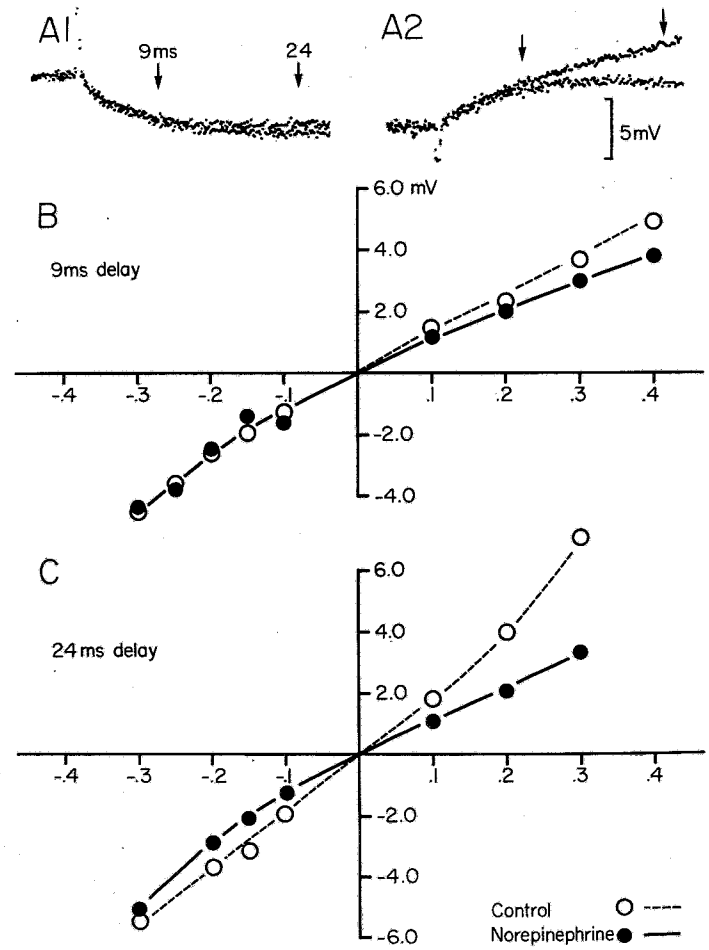

FIG. 5. Non-linear effect of NA on input resistance. (A) Average of 5 responses to identical hyperpolarizing (A1) and depolarizing (A2) current pulses. Whereas NA caused a large reduction of the depolarizing response, the hyperpolarizing response was hardly reduced below noise level. (B and C) Voltage deflections due to current pulses (ordinate) plotted against current strength (abscissa). Measurements made at 9 (B) and 24 msec (C) delay. When measured at 9 msec delay (B) there was no change in responses to hyperpolarizing pulses. When measured at 24 msec delay (C) there was a small reduction of responses to hyperpolarizing, but a more pronounced (about 50%) reduction of responses to depolarizing pulses. (From Langmoen *et al.*, 1981).

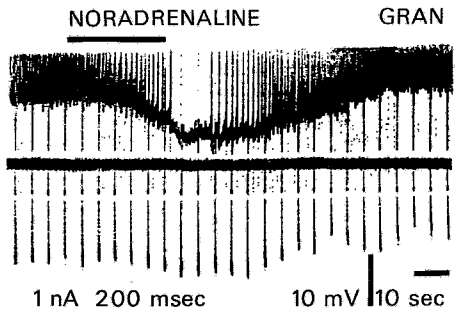

FIG. 6. Effect of noradrenaline on a dentate granule cell in a hippocampal slice of the rat. Noradrenaline was ejected by pressure during the time indicated by the bar above the trace into the dendritic area of the cell. The membrane potential is hyperpolarized, the conductance is slightly increased (reduction of the hyperpolarizing current pulses, 1 nA, interrupted by current monitor trace), and the spontaneous firing is depressed (upward deflections are clipped action potentials).

1977), the more recent suggestion that lithium interferes with the Na-K pump, thereby depolarizing cells and increasing release of transmitters in the hippocampus (Haas, 1982), offers an explanation for the lithium–NA antagonism.

In summary, NA hyperpolarizes and decreases excitability of hippocampal pyramidal and dentate granule cells. Three modes of action are suggested: (1) A conductance increase involving probably chloride ions. (2) A block of anomalous rectification (reduction in Na^+ and Ca^{2+} inward movements). (3) An activation of an electrogenic Na^+–K^+-pump. These mechanisms reduce the spontaneous activity and the effect of slowly increasing excitation but EPSPs from synchronized inputs can pass largely unchanged. In this way the signal-to-noise ratio of rapid information transfer is enhanced (Langmoen *et al.*, 1981).

V. Dopamine (DA)

According to Swanson and Hartmann (1975) a significant part of the catecholamine fluorescence in the hippocampal formation could be due to DA rather than NA, as DA-betahydroxylase, visualized by immunohistochemistry, shows a different distribution. DA-containing fibers show a typical distribution pattern in each brain area (Hökfelt *et al.*, 1974). In the hippocampal formation they seem to be concentrated in the hilus fasciae dentatae (see Storm–Mathisen, 1977a,b). A distinct dopaminergic pathway however, has not been traced.

Ionophoretically-applied DA depresses the firing of extracellularly recorded hippocampal neurons in the cat (Herz and Nacimiento, 1965; Biscoe and Straughan, 1966; Stefanis, 1968). Herrling (1981) found a hyperpolarization associated with a conductance decrease and a reduction of the amplitude of action potentials and EPSPs. On granule cells in rat hippocampal slices, Gmelin (1981) observed an excitatory action with bath-applied DA which was blocked by fluphenazine.

VI. Serotonin (5-HT)

Serotonin (5-HT) containing neurons from the median raphe nucleus project to the whole hippocampal formation with a certain concentration in the stratum lacunosum-moleculare of CA1 and close to the somata of granule cells (Kuhar *et al.*, 1972; Conrad *et al.*, 1974; Fuxe and Jonsson, 1974; Segal and Landis, 1974; Storm–Mathisen and Guldberg, 1974; Moore and Halaris, 1975; Azmitia and Segal, 1978; for details see Storm–Mathisen, 1977a,b).

Ionophoretically applied 5-HT depresses the firing of hippocampal neurons (Stefanis, 1964; Herz and Nacimiento, 1965; Biscoe and Straughan, 1966). Segal (1975, 1976) demonstrated a reduction of depressions induced by raphe stimulation or 5-HT ionophoresis by 5-HT antagonists (methysergide, cyproheptadine) and a potentiation of both responses by a 5-HT uptake blocker (chlorimipramine). Furthermore, in animals pretreated with *p*-chlorophenylalanine (PCPA, an inhibitor of 5-HT synthesis), raphe stimulation failed to produce a depression of firing and this action was alleviated by 5-HT or 5-hydroxytryptophane administration. Although the pathway could not be clearly characterized and the 5-HT antagonists have unspecific actions (Segal, 1976; and own observations), these results are consistent with the role of 5-HT as an inhibitory transmitter released from raphe fibers projecting to the hippocampus.

Intracellular recording in slices from neurons in the CA1 pyramidal layer revealed an hyperpolarizing action of 5-HT associated with a conductance increase (Cobbett and Cottrell, 1980; Jahnsen, 1980; Segal, 1980; Haas, 1981b). This effect is also present in synaptic isolation and is therefore postsynaptic. It seems to be maximal when 5-HT is applied close to the soma. Jahnsen (1980) also observed depolarizing and mixed responses. The membrane-permeability increase is probably to potassium ions in CA1 as the 5-HT responses are independent of the extracellular chloride concentration (Segal, 1980). This is substantiated by the experiments of Segal and Gutnick (1980) with ion selective electrodes, suggesting activation by 5-HT of sodium and calcium independent potassium channels (see Fig. 7).

Crunelli and Kelly (this volume), however, found a similar reversal

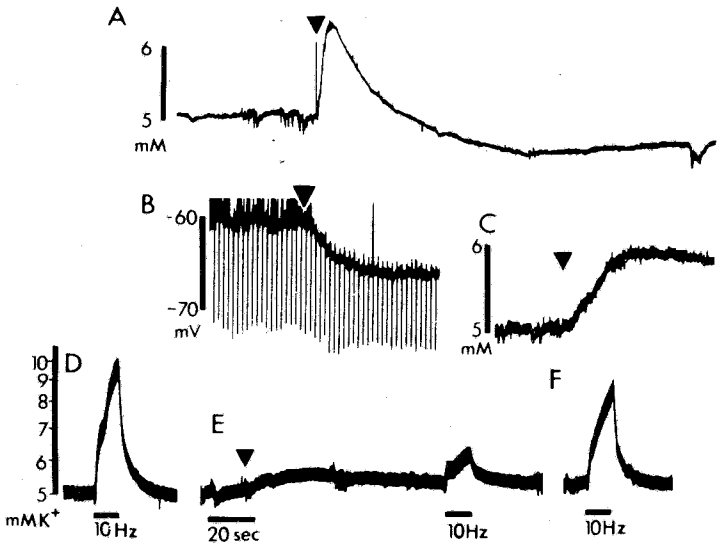

FIG. 7. Extracellular potassium concentration, K^+_o in CA1 and intracellular recording from a pyramidal cell. (A) A biphasic effect of 5-HT (arrow) on $[K^+]_o$. An initial rise in $[K^+]_o$ is followed by an apparent long-lasting "undershoot". The fast rise and fall time in this record is not typical. (B and C) The similarity in the time course of the effects of 5-HT on membrane potential and input resistance (B) and changes in $[K^+]_o$ (C). In B, the membrane potential hyperpolarizes from its resting level of -60 mV to about -66 mV. A corresponding 35 % reduction in input resistance, measured by the potential deflection produced by a 0.5 nA constant current hyperpolarizing current pulse, is evident. (D–F) Effects of 5-HT on the rise in $[K^+]_o$ produced by repetitive stimulation of the stratum radiatum. The stimulation produced a sharp rise in $[K^+]_o$ (D), 5-HT caused a moderate and slow rise in $[K^+]_o$ (E), but now the stimulation failed to produce the rise in $[K^+]_o$. Following recovery from 5-HT effects, the stimulation-induced $[K^+]_o$ changes have also recovered (F). The scale in E is the same for all traces, ordinate is mM K^+. (From Segal and Gutnick, 1980.)

potential for 5-HT and GABA actions on dentate granule cells, indicating a chloride dependent mechanism.

In summary, 5-HT hyperpolarizes most principal cells in the hippocampal formation. It presumably causes a conductance-increase to potassium (and chloride) ions. In this way brainstem raphe neurons can reduce the activity of pyramidal and granule cells and the effect of other afferent fibers.

VII. Conclusions

The internal circuitry in the hippocampal formation consists of a sequential excitatory connection from the entorhinal cortex via the area dentata and the

fields CA3 and CA1 to the subiculum and back to the entorhinal area (Andersen, 1975). The transmitters used by these "rapid" synapses are presumably excitatory amino acids (glutamate or aspartate: see Wieraszko, this volume, and Storm-Mathisen, 1977a,b). There is a large number of projections leaving or entering this circuit (Swanson, this volume) and some of the latter presumably release the substances described in this article, thereby modulating the functions of the circuit. Table I summarizes the possible actions.

TABLE I. Possible mechanisms for amine transmitter actions on principal cells in the hippocampal formation.[a]

	Source	Vm	g	Pump	Mediator	Presynaptic
ACh	medial septum	+	K ↓ Ca↑	no	c-GMP	yes
HA	supra-mammill.	– (+)	K ↑ Ca↓	yes	c-AMP	yes
NA	area locus coeruleus	–	K Cl↑ Ca↓	yes	c-AMP	?
DA	brainstem	–	K ↓	yes	c-AMP	?
5-HT	median raphe	– (+)	K ↑ Cl↑ Ca↓	yes	?	?

[a] Vm: membrane potential, +: depolarization, –: hyperpolarization. g: membrane conductance, suggested increase or decrease of potassium, calcium or chloride ion fluxes.

Electrical stimulation of fibers containing amine transmitters and their local application evoke directly measurable effects on the membranes of hippocampal pyramidal and dentate granule cells. These experiments create necessarily rather artificial situations. Input pathways are not naturally operating with a synchronous activation of many fibers and, considering the sparsity and specific distribution of aminergic fibres, the naturally released amines may never have the actions on the whole cell which are seen in ionophoretic experiments. However, as amines also seem to be released from non-synaptic varicosities, they may diffuse to a wide area and reach receptors on different cell bodies and axons. Such a mechanism of action is mimicked much more closely than "classical" neurotransmission by local application from micropipettes. The complex situation is difficult to elucidate but a dissection of the various implications has begun. All amines affect the postsynaptic membrane directly as synaptic isolation does not prevent their action. From these effects, although measured in a non-natural situation,

their function may be deducted. Conductance changes in the dendritic trees can very effectively control the response of a neuron to an input: an increase shunts synaptic potentials while a decrease enhances their impact. This mechanism is used locally by interneurons releasing GABA (Andersen *et al.*, 1981) and probably by the aminergic fibers originating from several brain areas. The action may be topically and functionally highly specific at axo-dendritic synapses. Future investigations, such as those already initiated by Adams *et al.* (1981) for ACh will need to analyse the nature of ionic currents more closely using voltage clamp experiments.

For some amines described here there is also evidence for presynaptic actions, probably not only on presynaptically situated interneurons but also on the effects on release and uptake sites. Voltage and conductance changes in presynaptic varicosities will undoubtedly influence transmitter release. Membrane pumps may be stimulated by several amines. Activation of the Na–K-pump leads to hyperpolarization and, on the presynaptic site, presumably to a reduction of transmitter release. Thus, in spite of the sparsity of aminergic fibers, it seems that amine transmitters significantly influence the hippocampal functions at several sites by a number of different mechanisms which await further exploration.

References

Adams, P. R., Brown, D. A. and Halliwell, J. V. (1981). Cholinergic regulation of M-current in hippocampal pyramidal cells. *J. Physiol.* **317**, 29.

Alvarez-Leefmans, F. J. and Gardner-Medwin, A. R. (1975). Influences of the septum on the hippocampal dentate area which are unaccompanied by field potentials. *J. Physiol.* **249**, 14.

Andersen, P. (1975). Organization of hippocampal neurons and their interconnections. *In*: "The Hippocampus" (Isaacson, R. L. and Pribram, K. H. eds), Vol. 1, pp. 155–175, Plenum, New York.

Andersen, P. and Lømo, T. (1969). Organization and frequency dependence of hippocampal inhibition. *In*: "Basic Mechanisms of the Epilepsies" (Jasper, H. H., Ward, A. A. and Pope, A. eds), pp. 604–609, Little Brown, Boston.

Andersen, P., Dingledine, R., Gjerstad, L., Langmoen, I. A. and Mosfeldt-Laursen, A. (1981). Two different responses of hippocampal pyramidal cells to application of GABA. *J. Physiol.* **305**, 279–296.

Azmitia, E. and Segal, M. (1978). The efferent connections of the dorsal and median raphe nuclei in the rat brain. *J. Comp. Neurol.* **179**, 641–668.

Barbin, G., Garbarg, M., Schwartz, J.-C. and Storm-Mathisen, J. (1976). Histamine synthesizing afferents to the hippocampal region. *J. Neurochem.* **26**, 259–263.

Benardo, L. S. and Prince, D. A. (1981). Acetylcholine induced modulation of hippocampal pyramidal neurones. *Brain Res.* **211**, 277–234.

Bird, S. J. and Aghajanian, G. K. (1976). The cholinergic pharmacology of hippocampal pyramidal cells: a microiontophoretic study. *Neuropharmacology* **15**, 273–282.

Biscoe, T. J. and Straughan, D. W. (1966). Microelectrophoretic studies of neurons in the cat hippocampus. *J. Physiol.* **183**, 341–359.

Bland, B. H., Kostopoulos, G. K. and Phillis, J. W. (1974). Acetylcholine sensitivity of hippocampal formation neurons. *Can. J. Physiol. Pharmacol.* **52**, 966–971.

Bliss, T. V. P. and Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiol.* **232**, 331–356.

Burchfiel, J. L., Duchowny, M. S. and Duffy, F. H. (1979). Neuronal supersensitivity to ACh induced by kindling in the rat hippocampus. *Science* **204**, 1096–1098.

Cobbett, P. and Cottrell, G. A. (1981). Actions of 5-hydroxytryptamine on CA1 pyramidal neurones of rat hippocampus *in vitro*. *J. Physiol.* **305**, 101.

Conrad, L. C. A., Leonard, C. M. and Pfaff, D. W. (1974). Connections of the median and dorsal raphe nuclei in the rat: an autoradiographic and degeneration study. *J. Comp. Neurol.* **156**, 179–206.

Dam Trung Tuong, M., Garbarg, M. and Schwartz, J.-C. (1980). Pharmacological specificity of brain histamine H_2-receptors differs in intact cells and cell-free preparations. *Nature, Lond.* **287**, 548–551.

DeFrance, J. F., Stanley, J. C., Marchand, J. E. and Chronister, R. B. (1977). Cholinergic mechanisms and short-term potentiation. *CIBA Found. Symp.* **158**, 109–126.

Dodd, J., Dingledine, R. and Kelly, J. S. (1981). The excitatory action of acetylcholine on hippocampal neurones of the guinea pig and rat maintained *in vitro*. *Brain Res.* **207**, 109–127.

Dudar, J. D. (1975). The effect of septal nuclei stimulation on the release of acetylcholine from the rabbit hippocampus. *Brain Res.* **83**, 123–133.

Fuxe, K. and Jonsson, G. (1974). Further mapping of central 5-hydroxytryptamine neurons: Studies with the neurotoxic dihydroxytryptamines. *In*: "Serotonin: New Vistas". (Costa, E., Gessa, G. L. and Sandler, M. eds). *Advances in Biochemical Psychopharmacology*, Vol. 10, pp. 1–12. Raven Press, New York.

Gähwiler, B. H. and Dreifuss, J. J. (1982). Multiple actions of acetylcholine on hippocampal pyramidal cells in organotypic explant cultures. *Neuroscience* 7, 1243–1256.

Garbarg, M., Barbin, G., Feger, J. and Schwartz, J.-C. (1974). Histaminergic pathway in the rat brain evidenced by lesions of the medial forebrain bundle. *Science* **186**, 833–834.

Gmelin, G. (1981). Effects of dopamine on granule cells in the hippocampal slice preparation. *Pflügers Arch. Suppl.* **391**, R 41.

Green, J. P., Johnson, C. L. and Weinstein, H. (1978). Histamine as a neurotransmitter. *In*: Psychopharmacology: A generation of progress (Lipton, M. A., DiMascio, A. and Killam, K. F. eds). Raven Press, New York.

Haas, H. L. (1981a). Histamine hyperpolarizes hippocampal neurones *in vitro*. *Neurosci. Lett.* **22**, 75–78.

Haas, H. L. (1981b). Analysis of histamine actions by intra- and extracellular recording in hippocampal slices of the rat. *Ag. Actions* **11**, 125–128.

Haas, H. L. (1982a). Cholinergic disinhibition in hippocampal slices of the rat. *Brain Res.* **233**, 200–204.

Haas, H. L. (1982b). Lithium and synaptic transmission in the mammalian brain. *In*: "Basic Mechanisms in the Action of Lithium" (Emrich, H. M., Aldenhoff, J. B. and Lux, H. D., Eds.). Excerpta Medica Int. Congr. Ser. 572, 71–79. Elsevier, Amsterdam.

Haas, H. L. and Geller, H. M. (1982). Electrophysiology of histaminergic transmission in the brain. *In*: "Occurrence, metabolism and pharmacological actions of histamine" (Tasaka, K. and Uvnäs, B. eds). "Advances in the Biosciences", Vol. 33, pp. 81–91. Pergamon Press, Oxford, 1982.

Haas, H. L. and Rose, G. (1981). Is disinhibition a component of hippocampal long term potentiation? *J. Physiol.* **318**, 27.

Haas, H. L. and Ryall, R. W. (1977). An excitatory action of iontophoretically administered lithium on mammalian central neurones. *Brit. J. Pharmac.* **60**, 185–195.

Haas, H. L. and Wolf, P. (1977). Central actions of histamine: microelectrophoretic studies. *Brain Res.* **122**, 269–279.

Haas, H. L., Wolf, P., Palacios, J. M., Garbarg, M., Barbin, G. and Schwartz, J.-C. (1978). Hypersensitivity to histamine in the guinea pig brain: microiontophoretic and biochemical studies. *Brain Res.* **156**, 275–291.

Heinemann, U., Lux, H. D. and Zander, K. J. (1978). Effects of norepinephrine and DB-cyclic-AMP on active uptake of K^+ in the cerebral cortex of cats. *In*: "Iontophoresis and transmitter mechanisms in the mammalian central nervous system" (Ryall, R. W. and Kelly, J. S., eds), pp. 419–428, Elsevier, Amsterdam.

Herrling, P. L. (1981). The membrane potential of cat hippocampal neurons recorded *in vivo* displays four different reaction mechanisms to iontophoretically applied transmitter agonists. *Brain Res.* **212**, 331–343.

Herz, A. and Nacimiento, A. C. (1965). Ueber die Wirkung von Pharmaka auf Neurone des Hippokampus nach microelektrophoretischer Verabfolg-ung. *Naunyn Schmied. Arch. Pharmacol.* **251**, 295–314.

Hökfelt, T., Ljungdahl, A., Fuxe, K. and Johansson, O. (1974). Dopamine nerve terminals in the rat limbic cortex: Aspects of the dopamine hypothesis of schizophrenia. *Science* **184**, 177–179.

Hotson, J. R., Prince, D. A. and Schwartzkroin, P. A. (1979). Anomalous inward rectification in hippocampal neurons. *J. Neurophysiol.* **42**, 889–895.

Hounsgaard, J. (1978). Presynaptic inhibitory action of acetylcholine in area CA1 of the hippocampus. *Exp. Neurol.* **62**, 787–797.

Jahnsen, H. (1980). The action of 5-hydroxytryptamine on neuronal membranes and synaptic transmission in area CA1 of the hippocampus *in vitro*. *Brain Res.* **197**, 83–94.

Kelly, J. S., Dodd, J. and Dingledine, R. (1979). Acetylcholine as an excitatory and inhibitory transmitter in the mammalian central nervous system. *Brain Res.* **49**, 253–266.

Krnjević, K. and Phillis, J. W. (1963). Actions of certain amines on cerebral cortical neurones. *Brit. J. Pharmacol.* **20**, 471–490.

Krnjević, K. Pumain, R. and Renaud, L. (1971). The mechanism of excitation by acetylcholine in the cerebral cortex. *J. Physiol.* **215**, 247–268.

Krnjević, K., Reiffenstein, R. J. and Ropert, N. (1980). Disinhibitory action of acetylcholine in the hippocampus. *J. Physiol.* **308**, 73.

Kuhar, M. J., Aghajanian, G. K. and Roth, R. H. (1972). Tryptophan hydroxylase activity and synaptosomal uptake of serotonin in discrete brain regions after midbrain raphe lesions: correlations with serotonin levels and histochemical fluorescence. *Brain Res.* **44**, 165–176.

Langmoen, I. A., Segal, M. and Andersen, P. (1981). Mechanisms of norepinephrine actions on hippocampal pyramidal cells *in vitro*. *Brain Res.* **208**, 349–362.

Lee, S. L. and Phillis, J. W. (1977). Stimulation of cerebral cortical synaptosomal Na–K–ATPase by biogenic amines. *Can. J. Physiol. Pharmacol.* **55**, 961–964.

Lewis, P. R., Shute, C. C. D. and Silver, A. (1967). Confirmation from choline acetylase analyses of a massive cholinergic innervation to the rat hippocampus. *J. Physiol.* **191**, 215–224.

Lynch, G., Mathews, D. A., Mosko, S., Parks, T. and Cotman, C. W. (1972). Induced acetylcholinesterase-rich layer in rat dentate gyrus following entorhinal lesions. *Brain Res.* **42**, 311–318.

Marshall, K. C. and Engberg, I. (1979). Reversal potential for noradrenaline-induced hyperpolarization of spinal motoneurons. *Science* **205**, 422–424.

Mellgren, S. I. and Srebro, B. (1973). Changes in acetylcholine-esterase and distribution of degenerating fibers in the hippocampal region after septal lesions in the rat. *Brain Res.* **52**, 19–36.

Moore, R. Y. and Halaris, A. E. (1975). Hippocampal innervation by serotonin neurons of the midbrain raphe in the rat. *J. Comp. Neurol.* **164**, 171–183.

Mosko, S., Lynch, G. and Cotman, C. W. (1973). The distribution of septal projections to the hippocampus of the rat. *J. Comp. Neurol.* **152**, 163–174.

Palacios, J. M., Wamsley, J. K. and Kuhar, M. J. (1981). The distribution of histamine H1-receptors in the rat brain. *Neuroscience* **6**, 15–37.

Pasquier, D. A. and Reinoso-Suarez, F. (1976). Direct projection from hypothalamus to hippocampus in the rat demonstrated by retrograde transport of horseradish peroxidase. *Brain Res.* **108**, 165–169.

Pickel, V. M., Segal, M. and Bloom, F. E. (1974). A radioautographic study of the efferent pathways of the nucleus locus coeruleus. *J. Comp. Neurol.* **155**, 15–42.

Sastry, B. S. R. and Phillis, J. W. (1977). Antagonism of biogenic amine-induced depression of cerebral cortical neurons by Na^+, K^+-ATPase inhibitors. *Can. J. Physiol. Pharmacol.* **55**, 170–179.

Segal, M. (1974). Lithium and the monoamine neurotransmitters in the rat hippocampus. *Nature, Lond.* **250**, 71–72.

Segal, M. (1975). Physiological and pharmacological evidence for a serotoninergic projection to the hippocampus. *Brain Res.* **94**, 115–131.

Segal, M. (1976). 5-HT antagonists in rat hippocampus. *Brain Res.* **103**, 161–166.

Segal, M. (1978). The acetylcholine receptor in the rat hippocampus: nicotinic, muscarinic or both? *Neuropharmacology* **17**, 619–623.

Segal, M. (1980a). Histamine produces a Ca^{2+}-sensitive depolarization of hippocampal pyramidal cells *in vitro*. *Neurosci. Lett.* **19**, 67–71.

Segal, M. (1980b). The action of serotonin in the rat hippocampal slice preparation. *J. Physiol.* **303**, 423–439.

Segal, M. (1981a). Histamine modulates reactivity of hippocampal CA3 neurons to afferent stimulation *in vitro*. *Brain Res.* **213**, 443–448.

Segal, M. (1981b). The action of norepinephrine in the rat hippocampus: intracellular studies in the slice preparation. *Brain Res.* **206**, 107–128.

Segal, M. and Bloom, F. E. (1974a). The action of norepinephrine in the rat hippocampus. I. Iontophoretic studies. *Brain Res.* **72**, 79–98.

Segal, M. and Bloom, F. E. (1974b). The action of norepinephrine in the rat hippocampus. II. Activation of the input pathway. *Brain Res.* **72**, 99–114.

Segal, M. and Bloom, F. E. (1976). The action of norepinephrine in the rat hippocampus. IV. The effects of locus coeruleus stimulation on evoked hippocampal unit activity. *Brain Res.* **107**, 513–525.

Segal, M. and Gutnick, M. J. (1980). Effects of serotonin on extracellular potassium concentration in the rat hippocampal slice. *Brain Res.* **195**, 389–401.
Segal, M. and Landis, S. (1974). Afferents to the hippocampus of the rat studied with the method of retrograde transport of horseradish peroxidase. *Brain Res.* **78**, 1–15.
Segal, M., Sagie, D. B. and Mayevsky, A. (1980). Metabolic changes induced in rat hippocampal slices by norepinephrine. *Brain Res.* **202**, 387–399.
Siggins, G. R., Oliver, A. P., Hoffer, B. J. and Bloom, F. E. (1971). Cyclic adenosine monophosphate and norepinephrine: effects on transmembrane properties of cerebellar Purkinje cells. *Science* **171**, 192–194.
Smith, C. M. (1974). Acetylcholine release from the cholinergic septo-hippocampal pathway. *Life Sci.* **14**, 2159–2166.
Stefanis, C. (1964). Hippocampal neurons: their responsiveness to microelectrophoretically administered endogenous amines. *Pharmacologist* **6**, 171.
Stefanis, C. (1968). Discussion of serotonin effects on central neurons. *Adv. Pharmacol.* **6A**, 414–418.
Steiner, F. A. (1968). Influence of microelectrophoretically applied acetylcholine on the responsiveness of hippocampal and lateral geniculate neurons. *Pflügers Arch.* **303**, 173–180.
Storm-Mathisen, J. (1974). Choline acetyltransferase and acetylcholinesterase in fascia dentata following lesion of the entorhinal afferents. *Brain Res.* **80**, 181–197.
Storm-Mathisen, J. (1977a). Localization of transmitter candidates in the brain: The hippocampal formation as a model. *Prog. Neurobiol.* **8**, 119–181.
Storm-Mathisen, J. (1977b). Localization of putative transmitters in the hippocampal formation. With a note on the connections to septum and hypothalamus. *Ciba Found Symp.* **158**, 49–86.
Storm-Mathisen, J. and Guldberg, H. C. (1974). 5-hydroxytryptamine and noradrenaline in the hippocampal region: effect of transection of afferent pathways on endogenous levels, high affinity uptake and some transmitter related enzymes. *J. Neurochem.* **22**, 793–803.
Swanson, L. W. and Hartman, B. K. (1975). The central adrenergic system. An immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-beta-hydroxylase as a marker. *J. Comp. Neurol.* **163**, 467–505.
Valentino, R. J. and Dingledine, R. (1981). Presynaptic inhibitory effect of acetylcholine in the hippocampus. *J. Neuroscience* **7**, 784–792.
Yamamoto, C. and Kawai, N. (1967). Presynaptic action of acetylcholine in thin sections from the guinea pig dentate gyrus *in vitro*. *Exp. Neurol.* **19**, 176–187.

Note added in proof

An interference by amines with the calcium-activated potassium conductance [gK(Ca)] in hippocampal pyramidal cells has recently been found. Dopamine augments after-hyperpolarizations due to gK(Ca) while acetylcholine, noradrenaline and histamine block gK(Ca) without affecting calcium spikes (Benardo, L. S. and Prince, D. A. (1982). *J. Neurosci.* **2**, 415–423; (1982) *Brain Res.* **249**, 333–344; Madison, D. V. and Nicoll, R. A. (1982) *Nature* **299**, 636–638; Haas, H. L. and Konnerth, A. (1983). *Nature* **302**, in press). By this mechanism the latter amines can profoundly potentiate excitatory responses.