THE PHARMACOLOGY OF CENTRAL AND PERIPHERAL INHIBITION

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I. INTRODUCTION

Throughout this review the term "inhibition" will be used in a rather restricted sense. Gasser (166) has given a general definition, but for present purposes "inhibition" will be used to describe a synaptic process at nerve or muscle cells which temporarily hinders excitation, and which is observed as a depression of the generation of impulses by these cells. This definition excludes postexcitatory depression, and the scope of the review will therefore be limited to the pharmacology of naturally occurring inhibitory transmitters and of the compounds which mimic, block, or potentiate the action of such substances.

Recent reviews have discussed in detail the physiology of inhibitory processes and pharmacological aspects of certain types of inhibition (100, 101, 102, 131, 143, 172, 195, 218, 326). Four types of inhibitory process can be included under the terms of the above definition. The first, "presynaptic" inhibition, involves a diminution in the amount of transmitter released from activated excitatory nerve terminals (96, 101, 102). Secondly, there may be a competitive antagonism for postsynaptic receptor sites between excitatory and inhibitory transmitter agents (133). Thirdly, postsynaptic inhibition involves an alteration in the membrane conductance beneath inhibitory synapses by the action of a transmitter substance, and this may or may not be accompanied by an alteration in membrane potential (102, 173). Finally, inhibitory action can be exerted by electrical current flow which hyperpolarizes the postsynaptic membrane (157, 161). In addition, another type of inhibition has been included which involves

the regulation of cellular metabolic processes associated with the maintenance of the membrane potential of cells (42). This is not strictly a synaptic process but nevertheless probably has functional significance.

II. CENTRAL INHIBITION

A. Vertebrate

1. Subcortical. Studies of the inhibitory processes in the vertebrate nervous system are most complete in the spinal cord. This is due mainly to the comparative ease with which neuronal responses can be recorded and measured, and to the ability to stimulate peripheral nerve fibres which have only an inhibitory action on the nerve cells under observation. Recent reviews deal with the pre- and postsynaptic inhibitory processes (101, 102, 103, 104, 173). Two factors contribute to the depression of neurone excitability by postsynaptic inhibition. As a result of the interaction between the chemical transmitter agent and the appropriate subsynaptic receptor sites, there is a transient increase in the permeability of the postsynaptic membrane to chloride ions and possibly also to potassium ions (8, 64, 106). This increase of conductance reduces the effect of depolarizing postsynaptic currents which are generated at activated excitatory synapses, and, if of sufficient intensity, prevents excitatory synaptic depolarization from reaching the threshold for the discharge of an impulse. In addition, inhibition is usually associated with a hyperpolarization of the membrane which sums algebraically with excitatory depolarizations and so counteracts excitation. The occurrence of a hyperpolarization indicates that the equilibrium potential for the ionic movements is more negative than the resting membrane potential. Hyperpolarizing inhibitory potentials have been observed in a variety of mammalian neurones (102) and also in amphibian spinal neurones (217, 223). In the case of the spinal motoneurone of the cat this change in membrane potential is unlikely to be an artifact introduced by the intracellular recording procedure, since it can be detected peripherally in the ventral roots after electrotonic propagation (7). In some cases, however, it is possible that the equilibrium potential for the inhibitory hyperpolarization is the same as the resting membrane level (see 101).

Although a detailed analysis of postsynaptic inhibition has been carried out only upon spinal motoneurones, and particularly with respect to "direct" inhibition of monosynaptic reflexes, it is highly probable that suppression of impulse generation in other vertebrate nerve cells is also produced by this inhibitory conductance change and hyperpolarization. In addition, however, another form of inhibition has been described—presynaptic inhibition. A chemical synaptic mechanism has been proposed by which impulses in certain peripheral afferent fibres and descending tracts eventually depolarize the synaptic terminals of other fibres located upon motoneurones, and in this way reduce the amount of synaptic transmitter released (6, 110, 112, 114). This process depresses the synaptic excitation of motoneurones (107, 113, 152, 153) without altering either the potential or the conductance of the postsynaptic membrane. As yet the only intensive investigation of presynaptic inhibitory mechanisms has been in the

spinal cord, but it is probable that this process is of fundamental importance in the operation of the nervous system, particularly in controlling the central action of impulses arising from peripheral receptor organs (see 102).

The nature of the chemical transmitter substances for both pre- and postsynaptic inhibition remains unknown, although attempts have been made to isolate transmitters from central nervous tissue (142, 255). The conditions to be met before a substance can be identified as a transmitter for postsynaptic inhibition have been defined (73). It is essential that the substance induce the same conductance change in the subsynaptic membrane beneath inhibitory synapses as does the transmitter. Furthermore, agents which either block synaptic transmission by preventing the interaction between the transmitter and postsynaptic receptor sites, or potentiate transmission by interfering with the enzymic inactivation of synaptically released transmitter, must have identical effects upon the action of the suspected transmitter. Similar conditions can be applied to the testing of chemical substances considered to be transmitters for presynaptic inhibition. In this case, however, it is necessary that these compounds diminish excitatory synaptic action by depolarizing presynaptic terminals, without affecting the postsynaptic membrane. In addition, the pharmacology of this process should be identical to that of presynaptic inhibition.

Factor I has been proposed as an inhibitory transmitter. This is extracted from mammalian brain (124, 139, 149), particularly from gray matter (147), and, although it is inactive when administered intraarterially, Factor I depresses spinal monosynaptic reflexes when applied topically to the cord (150, 185). The depression is transient and may be followed by potentiation. Polysynaptic reflexes, on the other hand, are increased in magnitude. The prior administration of subconvulsive doses of strychnine reduces the depression of monosynaptic reflexes by Fraction A of Factor I, but strychnine is relatively ineffective upon the action of Fraction B (150, 185, 254). Factor I also depresses transmission through sympathetic ganglia (149) and the nucleus gracilis (185). Recently, it has been reported that, when applied topically to the spinal cord, Factor I hyperpolarizes motoneurones, reduces the magnitude of inhibitory and excitatory postsynaptic potentials, and blocks orthodromic spike production (255). Consequently a component of Factor I may be considered as a possible inhibitory transmitter acting upon mammalian spinal motoneurones, although final confirmation of this inhibitory action must await its administration near single motoneurones.

One of the substances sometimes present in extracts containing Factor I is γ-amino-*n*-butyric acid (GABA) (14, 123, 252, 253, 254). This amino acid, and closely related substances such as γ-amino-β-hydroxybutyric acid (GABOB) (251), β-guanidinobutyric acid, and γ-aminobutyrylcholine (185), do not depress spinal monosynaptic reflexes when applied topically to the spinal cord, even in comparatively high concentrations. Furthermore, although GABA and closely related neutral amino acids including GABOB depress the activity of spinal neurones when ejected electrophoretically near single cells (82, 85), these substances do not alter the resting membrane potentials of motoneurones. In addition, the depressant action of the amino acids is not prevented by strychnine

(85). Similarly, strychnine does not reduce the depression of extensor monosynaptic reflexes produced by the intravenous administration of GABA or β-alanine in unanaesthetized spinal cats (224, 285). It is therefore unlikely that either GABA or GABOB is a transmitter for postsynaptic inhibition within the mammalian spinal cord (83), although a role in presynaptic inhibition has not yet been excluded.

Other inhibitory factors have been extracted from mammalian brain tissues and these bear some similarity to Factor I (see 255). One of these factors (233, 234, 235) has a depressant action upon spinal reflexes. The chromatographic properties of this substance are similar to those of GABA, but the two substances differ when tested upon the cerebral cortex or upon acetylcholine contractions of the isolated ileum of the cat. Another extract (292, 297) has not been tested for its effect upon the central nervous system. It has also been reported that an ethanol extract of brain has a depressant action similar to that of GABA upon neurones of the mammalian hypoglossal nucleus (205).

Many substances have been considered as possible inhibitory transmitters because of their presence in central nervous tissue and their depressant action upon some portion of the central nervous system. Substance P (162, 176a, 295) is present in subcellular particles isolated from nervous tissue (203, 317) and crude extracts have been reported to cause sedation in rabbits and cats after intraventricular injection (361) and mice after subcutaneous administration (383). This substance also depresses polysynaptic spinal reflexes following intravenous injection (332) and apparently can hyperpolarize cortical neurones (57), although this hyperpolarization has not been measured directly. Substance P antagonizes convulsions evoked by strychnine, Metrazol (pentamethylenetetrazol) and picrotoxin (383, 384, 385), and it is of interest that strychnine and *d*-lysergic acid diethylamide have been reported to inhibit enzymes responsible for the inactivation of substance P (203, 214). In the presence of *d*-lysergic acid diethylamide, substance P enhances dorsal root potentials in decerebrate cats (214), a finding which, taken in conjunction with the high concentration of this substance in dorsal root fibres (211, 227), may suggest a role of this agent in presynaptic inhibition. This is unlikely, however, since presynaptic inhibition is not exerted directly by impulses in primary afferent fibres (110). It is unknown to what extent impurities in substance P extracts account for these various observations, and, although pure samples of this agent have not yet been tested directly upon single nerve cells, the comparative inactivity of highly purified samples upon the nervous system (176a) suggests that substance P is unlikely to be a synaptic transmitter (see also 227a).

Adrenaline and noradrenaline are also present in nervous tissue (54, 360) but the reported effects of these substances upon neurones are extremely variable (315). These results may reflect the relative impermeability of the blood-brain barrier to the catecholamines. There is no direct evidence that the depression of spinal reflexes evoked by these substances (15, 46, 256, 280, 322, 328) is due to pre- or postsynaptic inhibition. No action was observed when these agents were administered electrophoretically to neurones in the spinal cord (86) or brain

stem (80), although, when they are administered intravenously or intraarterially, neurones in both regions have been reported to be sensitive to these compounds (22, 329). Feldberg (134) has suggested that the anaesthetic-like effect which follows intraventricular injection of adrenaline and noradrenaline may be due to inhibition of paraventricular neurones. Another suggestion is that the effects of systemically administered catecholamines upon spinal reflexes may be due to stimulation of the bulbar reticular formation (69, 328).

Another catecholamine in the central nervous system, 3-hydroxytyramine (dopamine) (54), diminishes the magnitude of monosynaptic reflexes when applied topically to the spinal cord in comparatively high concentrations. The effect is prevented by strychnine and by an adrenergic blocking agent, 1-(3,4-dichlorophenyl)-2-*iso*-propylaminoethanol hydrochloride (dichloro-*iso*-proterenol, DCI), but the latter substance has no action on the direct inhibition of spinal reflexes (257). Since DCI diminishes the reduction of spinal reflexes evoked by stimulation of the reticular formation (256), it has been suggested that this agent and 3-hydroxytyramine act upon spinal inhibitory interneurones that are on the pathway between the reticular formation and motoneurones. In agreement with this suggestion, topically applied 3-hydroxytyramine has been reported to increase the excitability of neurones near or in the intermediate nucleus, which also respond to stimulation of the reticular formation (257). When tested by the electrophoretic technique, however, 3-hydroxytyramine not only failed to depress the orthodromic and antidromic firing of motoneurones, but also was without action upon Renshaw cells and a variety of spinal interneurones (74). There is thus no satisfactory explanation of the depressant action of this catecholamine, which may be a component of Factor I (256).

5-Hydroxytryptamine and a large series of structurally related indoles antagonize the excitation of neurones in the lateral geniculate nucleus by volleys in the optic tract (77). These agents are unlikely to be postsynaptic inhibitory transmitters, since there appears to be no change in the conductance of the postsynaptic membrane. However, a presynaptic mode of action, similar to that of a transmitter for presynaptic inhibition, has not been excluded. There is as yet no satisfactory explanation of the sedation which follows the intraventricular administration of 5-hydroxytryptamine, *d*-lysergic acid diethylamide, and related substances (21, 164, 260). The diminution of spinal reflexes by 5-hydroxytryptamine (330, 367, 368) does not seem to be associated with a direct neuronal action of this substance (see 86).

Acetylcholine does not affect the excitability of spinal motoneurones when administered electrophoretically, and this substance and other choline esters have no action upon spinal interneurones, apart from Renshaw cells (86). Consequently, in the many investigations where acetylcholine or related substances have depressed spinal monosynaptic reflexes (43, 84, 230, 323, 324, 325, 338, 355), it is probable that the depression was produced by the excitation of Renshaw cells, which are known to have cholinoceptive receptors (78, 105, 108) and which exert a powerful inhibitory action on motoneurones (108). Atropine has no effect upon the direct inhibition of spinal monosynaptic reflexes (63).

A considerable number of investigations has been concerned with the effect of strychnine upon spinal reflexes (28, 97), but it was not until a study was made of the effect of this agent upon the "direct" inhibition of motoneurones that a clear finding emerged. Prior to this investigation the general features of strychnine action were described in great detail and three possible modes of action were suspected: a conversion of inhibition into excitation; an augmentation of synaptic excitation (290, 327); and a direct action on the membrane of cells (28, 35, 59, 320). Many of these early investigations were complicated by the use of mixed inhibitory and excitatory volleys during the testing procedure, and by the generalized effect of intravenously administered or topically applied strychnine.

The simplest inhibition of spinal motoneurones, "direct" inhibition, is obtained by stimulating the lowest threshold afferent fibres from muscles of antagonistic function (236). The inhibition can be observed either as a depression of monosynaptic reflexes (20, 336) or by recording an intracellular hyperpolarization (33, 64). A detailed analysis of this inhibition has shown that an interneurone is interposed between the primary afferent fibres and the inhibited motoneurones (7, 109). Subconvulsive doses of strychnine (up to 0.1 mg/kg intravenously in the anaesthetized cat) reduce the amount of inhibition of reflexes and the magnitude of the relayed inhibitory hyperpolarization, yet do not affect conduction in peripheral nerve fibres or monosynaptic excitatory action (20, 65, 72). Bradley *et al.* (20) concluded that strychnine either competed with the synaptically released inhibitory transmitter for subsynaptic receptor sites or prevented the ionic movements associated with the inhibitory conductance change. Since strychnine does not alter potentials generated by the interneurone on the direct inhibitory pathway (72), it was concluded that it does not block this type of inhibition by depressing inhibitory interneurones. Supporting evidence is provided by the finding that recurrent inhibition is also reduced by strychnine (108), which has either no effect or a slight potentiating action on the cholinoceptive Renshaw cells of this inhibitory pathway (105). Although strychnine has been reported to modify the properties of nerve fibres (67, 129, 181, 296), it is unlikely that the specific depression of inhibition produced by comparatively low concentrations of the alkaloid would be associated with effects upon the terminals of inhibitory nerve fibres. Wall *et al.* (363) have suggested that strychnine hyperpolarizes and increases the threshold of the terminal arborizations of primary afferent fibres in the ventral horn. In that case, two conflicting effects could be involved: a small hyperpolarization might increase the amount of transmitter released by an impulse (111, 188) but a larger hyperpolarization could actually prevent impulse transmission in the terminal arborizations of the fibres. Comparatively large doses of strychnine were administered in these experiments (363) and the change in afferent fibre threshold would of necessity have involved those fibres concerned in the monosynaptic excitation of motoneurones. However, when strychnine is administered intravenously (65, 72) or by electrophoretic ejection near single motoneurones (75), concentrations adequate to abolish inhibitory hyperpolarizations do not depress monosynaptic excitation. In addition, the local administration of strychnine near spinal motoneurones does not

change the membrane potential of these cells (75). This indicates that there is no direct excitatory effect upon the postsynaptic membrane (28, 35, 59, 320). Thus it can be assumed that strychnine has three possible effects: 1) it prevents the release of inhibitory transmitters from presynaptic terminals, 2) it prevents access to subsynaptic receptor sites, or 3) it interferes with the movement of ions through activated inhibitory subsynaptic membrane.

In addition to "direct" and recurrent inhibition, other types of purely spinal inhibition in the cat and toad are also reduced by strychnine (20, 72, 75, 223). Furthermore, the inhibitions of lumbar motoneurones by afferent volleys initiated in forelimb nerves and by stimulation of the anterior lobe of the cerebellum are diminished (72). Investigations of inhibitory processes elsewhere in the vertebrate nervous system are less complete, and it is unknown to what extent the effect of strychnine upon higher centres is produced by a depression of postsynaptic inhibition (308). Strychnine does, however, diminish the inhibitory action which impulses in the olivo-cochlear bundle exert on the receptor terminals of the hair cells of the organ of Corti (95). The inhibition of the Mauthner cell of the goldfish is also depressed by strychnine (160); the "late collateral inhibition," which is associated with an increase of membrane permeability, appears to be more susceptible than the inhibition produced by electrical synaptic transmission (157, 161).

The alkaloids thebaine (131, 302) and bruceine (75) also diminish the postsynaptic inhibition of mammalian spinal motoneurones; both are less potent than strychnine. Morphine and codeine, which are closely related to thebaine, are inactive (302). These alkaloids are of complex structure and several groups of synthetic agents are of considerable interest because of the relatively simple molecules which are involved (243a). However, sufficient evidence is not available to indicate the molecular features necessary for the diminution of inhibition. A series of diazadamantane derivatives has strychnine-like properties (243a), particularly 5,7-diphenyl-1,3-diazadamantan-6-ol, which depresses the inhibition of spinal motoneurones (75, 243, 245). 4-Phenyl-4-formyl-N-methylpiperidine has a similar action upon inhibition (75, 244), an effect which is presumably shared by some closely related compounds which produce convulsions similar to those evoked by strychnine (243a). Another substance, hexahydro-2′-methylspiro[cyclohexane - 1 , 8′(6H) - oxazino(3 , 4 - A)pyrazine], has strychnine-like actions (61a) and reduces spinal direct inhibition (75a). When injected intravenously, picrotoxin, pentamethylenetetrazol, β-methyl-β-ethylglutarimide, tubocurarine, and meperidine do not influence spinal inhibitions (63, 72, 75a).

Sherrington (327) noted the similarity between the central actions of strychnine and tetanus toxin. When injected into either a motor nerve or directly into the spinal cord, this toxin depresses the inhibition of spinal motoneurones (37, 72, 380). As with strychnine, tetanus toxin depresses a wide variety of postsynaptic inhibitions when it is injected into the spinal cord: the direct inhibition of motoneurones by impulses in the group Ia afferent fibres of antagonistic muscles; the inhibition by impulses in the group Ib afferent fibres from muscles in the same limb; the inhibition of extensor motoneurones by impulses in the

groups II and III muscle afferent fibres and in cutaneous afferent fibres; the recurrent inhibition of motoneurones; the descending inhibition produced by stimulating the anterior lobe of the cerebellum. It is probable that a similar diminution of inhibition accounts for the action of tetanus toxin in frogs (316) and lizards (68).

The precise mode of action of tetanus toxin is unknown. In the mammalian spinal cord the failure of this agent to influence the inhibitory interneurones upon both the direct and recurrent inhibitory pathway suggests that the site of action is near motoneurones (37). Because of the similarity between this toxin and botulinum toxin (382), it has been proposed that tetanus toxin interferes with the production or the release of inhibitory transmitters. On the other hand the toxin might also prevent the access of these transmitters to postsynaptic receptor sites. Van Heyningen (356) has attempted to identify the substance upon which the toxin acts at inhibitory synapses. A ganglioside has been extracted (357) which combines not only with tetanus toxin, strychnine, brucine, and thebaine, but also with 5-hydroxytryptamine and tryptamine (358). This substance does therefore not appear to be specifically related to compounds capable of depressing spinal inhibition.

Pharmacological studies on the presynaptic inhibition of mammalian lumbar motoneurones (115) have shown that it is unaffected or even increased by doses of strychnine that are adequate to suppress postsynaptic inhibition. In contrast, presynaptic inhibition is reduced by picrotoxin, although comparatively large doses do not suppress presynaptic inhibition to a degree comparable with the effect of strychnine upon postsynaptic inhibition. β-Methyl-β-ethylglutarimide had little or no depressant action and pentamethylenetetrazol was ineffective even in large doses. It has been suggested that picrotoxin competes with receptor sites for the presynaptic inhibitory transmitter substance, a postulate which leads to the conclusion that different transmitter substances are involved at the synapses for pre- and postsynaptic inhibition. The presynaptic inhibition of spinal reflexes is increased and prolonged by barbiturates and chloralose, a finding which has been ascribed either to depression of an enzyme that destroys the presynaptic inhibitory substance or to an enhancement of diffusional barriers at presynaptic inhibitory synapses (115). Dihydro-β-erythroidine, atropine, gallamine triethiodide, nicotine, tetraethylpyrophosphate, and eserine are without action upon presynaptic inhibition; hence acetylcholine is unlikely to be the transmitter (115).

The depression of postsynaptic inhibition by strychnine and related agents is probably a sufficient explanation of the observed effects of these substances upon the central nervous system (20, 72, 131): the increase in polysynaptic spinal reflexes (201, 286, 320), the occasionally observed increase in monosynaptic reflexes (20, 243, 244, 245), the production of spontaneous rhythmical bursts of excitation (strychnine tetanus) (29, 35, 193, 223), and the excitatory action upon the cerebral cortex (308). However, there are many reports in the literature of inhibitory actions apparently resistant to strychnine. These include inhibitory systems restricted entirely to local portions of the brain stem or spinal cord (66, 70, 93, 231) as well as those dependent upon conduction in descending

tracts from higher centres (24, 25, 30, 258). In particular, the convulsive activity of spinal segments evoked by strychnine can still be inhibited by stimulation of the reticular formation, the cerebellum, the vestibular apparatus, and neck proprioceptors (25, 26, 27, 28, 29, 30, 167, 318, 340, 341, 344). One common feature of the inhibitions listed above is that they are exerted through polysynaptic pathways, and two factors are probably involved in the failure of strychnine to reduce these inhibitory actions. In the first place, the depression of postsynaptic inhibition at synaptic relays upon a polysynaptic inhibitory pathway may result in an intensification of the final inhibitory synaptic action upon motoneurones, which would counteract the blocking action of strychnine. This explanation was proposed to account for the observation that the depression of direct inhibition by strychnine is usually much greater than that of the other forms of spinal inhibition which are produced by volleys in higher threshold muscle and cutaneous afferent fibres (20, 72). When strychnine was administered in the immediate vicinity of motoneurones, the direct and polysynaptic inhibitions appeared to be reduced to the same extent (75).

The other explanation of these strychnine-resistant inhibitions is that they are of the presynaptic type. Thus it is probable that the inhibition of stretch reflexes produced either by pulling on knee flexor muscles (231) or by active contraction of these muscles (66) is presynaptic in origin, and exerted by impulses in group I afferent fibres (113). Furthermore, descending volleys from the cerebrum (6, 56), brain stem (55), and bulbar reticular formation (249) have a presynaptic inhibitory action upon spinal reflexes, and it is probable that a similar effect follows stimulation of the anterior lobe of the cerebellum (342, 343). If it is assumed that these various forms of presynaptic inhibition are all resistant to strychnine (115), then these observations provide a ready explanation for the inhibition of strychnine tetanus of the spinal cord which is produced by stimulating higher centres. However, it is probable that with many of these descending inhibitory pathways a mixture of pre- and postsynaptic inhibition is exerted on spinal motoneurones, because both strychnine and tetanus toxin have a depressant effect upon the inhibition of spinal reflexes evoked by cerebellar stimulation (72), and strychnine reduces the inhibition produced by stimulating the reticular formation (256).

2. Cortical. Although in many cases a report of "inhibition" of cortical neurones means merely that a temporary arrest of unit discharges has been observed (see 4), hyperpolarizing potentials have been recorded from cells of the cerebral cortex (1, 2, 23, 284, 298, 299, 300), the cerebellar cortex (171), and the hippocampus (202). The apparent excitatory action of strychnine upon cortical neurones (59, 60, 228) has been attributed to a suppression of postsynaptic inhibition (308). The presence of inhibitory hyperpolarizing synapses in both the cerebral and cerebellar cortices has been analysed by a pharmacological technique (305, 306, 309, 310), the results of which have been taken to indicate that postsynaptic inhibition is not present in the cerebellar cortex to the same extent as it is in the cerebral cortex. This technique is based on three assumptions: that GABA selectively inactivates excitatory axodendritic synapses; that ϵ-aminocaproic acid and ω-aminocaprylic acid selectively inactivate inhibitory axo-

dendritic synapses; and that strychnine inactivates all inhibitory synapses (309). Such specific effects of the amino acids could not be demonstrated when the compounds were applied electrophoretically to spinal neurones (83, 85), and alternative suggestions have been offered for the observed effect of GABA on potentials recorded from the surface of the brain (16, 194, 196, 197, 259). Furthermore, if the "inhibitory" action of electrophoretically administered GABA on cortical neurones (215) proves to have a mechanism similar to that of the depressant action of this substance upon spinal neurones (85), the hypothesis concerning its specific blocking of excitatory synapses becomes untenable. In that case it is probable that this pharmacological method of analysing cortical potentials into excitatory and inhibitory components is misleading.

When applied topically to the cerebral cortex (60, 136) and to the isolated toad spinal cord (99, 208), tubocurarine has an excitatory action similar to that of strychnine. It has been proposed that, when administered intraarterially or intravenously, tubocurarine blocks inhibitory synapses in the cerebral cortex (283, 307, 308), although no effect of smaller doses could be demonstrated upon neurones in an isolated section of the cerebral cortex (311). It is possible that the observed effects of comparatively large doses of tubocurarine upon cortical responses are indirect (31), and that this substance may even excite some cortical neurones (216; see also 76). Tubocurarine has no action upon the direct inhibition of spinal monosynaptic reflexes (72) and probably fails to penetrate the blood-brain barrier of the spinal cord (79).

The recurrent inhibition of cortical neurones produced by impulses in collaterals of pyramidal axons (298, 299) is depressed by tetanus toxin (36), but the report (284) that this inhibition is blocked also by strychnine and picrotoxin, and that the recurrent pathway is cholinergic, has not been confirmed.

When injected into the ipsilateral carotid artery, 5-hydroxytryptamine, adrenaline, noradrenaline, iproniazid, amphetamine, bufotenine, mescaline, adrenochrome, GABA, and uncharacterized extracts of human serum diminish the amplitude of negative potentials recorded from the cerebral cortex in response to stimulation of the optic tract or the contralateral cerebral cortex (180, 265, 268, 269, 270, 271, 272, 274, 315). On the assumption that the observed diminution of evoked cortical potentials is produced by an inhibition of cortical neurones, it has been suggested that adrenaline, noradrenaline, and 5-hydroxytryptamine are synaptic inhibitory transmitters: the site of action of GABA differs from that of the other compounds (269). The main basis for this proposal is that certain components of a potential evoked by stimulating the contralateral cerebral cortex are produced monosynaptically, and represent postsynaptic potentials of cortical neurones (see 268). However, this transcallosal pathway is probably not monosynaptic, and the nature of the positive and negative components of the evoked potential has been questioned (226). There is no direct evidence that these substances are in fact acting as inhibitory transmitters upon cortical neurones, and the observed depression of cortical potentials may arise from a combination of several factors. For example, stimulation of extracerebral receptors such as those of the carotid sinus can affect potentials

recorded from the cortex (19, 209, 287); in addition, the intraarterially injected drugs may also modify the activity of brain-stem neurones (91) and thus indirectly affect the cortex. Furthermore, the observed depression of the synaptic responses of cortical neurones need not necessarily be produced by an inhibitory action, but may merely reflect a depression of synaptic excitatory processes, such as has been observed in the lateral geniculate nucleus (77). It is of interest in this respect that cortical responses are diminished not only by 5-hydroxytryptamine, adrenaline, and noradrenaline, but also by *d*-lysergic acid diethylamide (266) and 2-bromo-*d*-lysergic acid diethylamide (176), all of which have a depressant action similar to that of 5-hydroxytryptamine on neurones of the lateral geniculate nucleus (77).

B. Invertebrate

Furshpan and Potter (159) have studied the "inhibitory" postsynaptic potentials recorded in the giant motor fibre of the abdominal nerve cord of the crayfish *Astacus fluviatilis*. These arise either spontaneously, or as the result of stimulating the dorsal surface of the nerve cord, and are accompanied by a change in the conductance of the postsynaptic membrane. It is presumed that a chemical transmitter is involved, and GABA (3 to 5 $\times$ 10^{-7} M) reproduced most of the actions of this agent without affecting the presynaptic fibre. Evidence has been presented that GABA and the transmitter affect the permeability of the postsynaptic membrane to the same ion or ions. This synaptic region is of great interest because excitatory postsynaptic potentials recorded from the same fibres appear to be the result of electrical synaptic transmission (158). It is not known to what extent the effects of various agents upon the giant motor synapses of *Cambarus clarkii* (319, 377, 378) and of nicotine on *Astacus* (158) are associated with these synaptic processes. One important finding is the relative ineffectiveness of strychnine, picrotoxin, and Metrazol on the nerve cord of *Cambarus* (282, 378). γ-Aminobutyric acid (10^{-2} M) has no effect upon the spontaneous activity of the abdominal ganglia of the crayfish *Orconectes virilis*, which are apparently excited by picrotoxin (182). Moore (281) reported on the effects of drugs upon the nerve cord of the earthworm, *Lumbricus terrestris*, and a series of agents have been injected directly into the thoracic ganglion of the grasshopper *Melanoplus femur-rubrum* (71). In both cases the comparatively high drug concentrations that were used make the results difficult to assess, but the excitant actions of picrotoxin and strychnine were so weak that these compounds are unlikely to affect inhibitory processes in these animals.

Tauc has made a clear distinction between two types of nerve cell in the abdominal ganglia of the sea slug, *Aplysia depilans*, and has suggested that the inhibitory synapses of the H cells (168, 336) operate by acetylcholine (337). Thus acetylcholine produces in the H cells an increase in the membrane conductance and a hyperpolarization which has an equilibrium potential identical with that of the synaptically produced inhibitory hyperpolarization (333). By ejecting acetylcholine electrophoretically from a micropipette, it was shown that the sensitivity of the H cells was maximal near the synaptic contacts upon

the proximal axonal membrane. The threshold concentration for acetylcholine was of the order of 7×10^{-12} M and the hyperpolarizations induced both synaptically and by acetylcholine were reduced in magnitude by tubocurarine (10^{-10} M) and atropine (10^{-10} M). Physostigmine (10^{-10} M) potentiated the action of acetylcholine but reduced the amplitude of inhibitory hyperpolarizations. It has been suggested (337) that physostigmine not only inhibits cholinesterase but also inactivates the postsynaptic cholinoceptive sites. These results, taken in conjunction with the earlier observation that the tissue contains acetylcholine (11), strongly suggest a role of acetylcholine as an inhibitory transmitter upon these cells. In contrast, other neurones, called D cells, were excited by this choline ester (337). Similar results have been reported for neurones in the visual ganglion of the snail *Helix pomatia* (335). In addition to the postsynaptic inhibition observed in *Aplysia*, a type of presynaptic inhibition occurs in both *Aplysia* and *Helix* (334) but the effect of chemical agents on this process has not been studied.

Hagiwara and Kusano (177) have investigated synaptic inhibition in the ganglion cells of the mollusc *Onchidium verruculatum*. The postsynaptic inhibitory potential has an equilibrium potential close to the resting potential. In concentrations of 10^{-2} M, GABA, β-alanine, and GABOB have no inhibitory action, whilst both gamma-aminobutyrylcholine and acetylcholine (5×10^{-4} M) produce an increase in membrane conductance without altering the membrane potential. It was suggested that the inhibitory action of γ-aminobutyrylcholine is related to the choline ester structure, rather than to the disposition of amino and carboxylic groups (177). Since relatively high concentrations of acetylcholine were needed to obtain an inhibitory effect, it is doubtful whether this is an inhibitory transmitter (177).

III. PERIPHERAL INHIBITION

A. Vertebrate

1. Heart. Similarities between Loewi's "Vagusstoff" (237, 241) and the acetyl ester of choline (87, 189) led to the identification of the vagal inhibitory transmitter as acetylcholine (38, 88, 135, 190, 238, 239). It has been shown for both amphibian and mammalian atrial and pacemaker tissue that vagal inhibition is associated with an increase in membrane conductance (348), and usually also with an increase in resting potential (165, 184, 192). Acetylcholine also increases the membrane conductance, probably by increasing the permeability to potassium ions (179, 191, 346), and produces changes in resting and spike potentials which are similar to those resulting from vagal stimulation (49, 58, 184, 199, 321, 347, 348, 374). Pilocarpine, muscarine, and other choline esters have a similar effect upon the heart (49, 87, 189, 364) but are not as potent as, and have a more prolonged action than, acetylcholine.

Further confirmation of the role of acetylcholine as a cardioinhibitory transmitter was provided by the finding that atropine, in small doses (10^{-6} M), blocked the effect both of vagal stimulation and of acetylcholine (39, 87, 165, 179, 189,

192, 240). Atropine has no effect upon the liberation of acetylcholine by vagal impulses (240) and is presumed to prevent the access of acetylcholine to postsynaptic receptors. However, as Shanes (326) has pointed out, atropine is also a membrane stabilizer and this "nonspecific" action must also be considered as an alternative possibility (see also 5, 81).

Dale (87) suggested that the brief duration of acetylcholine action might be associated with its hydrolysis, and Loewi's findings indicated that the choline ester was destroyed by an esterase which was inhibited by physostigmine (128). Thus the action of acetylcholine upon the frog heart (242) and upon the rabbit atrium (366) is intensified and prolonged by physostigmine (see also 51). Furthermore, when administered in doses which were adequate to reduce the rate of hydrolysis of acetylcholine by cholinesterase (276), physostigmine prolonged and intensified vagal inhibition of the heart (39). Although both amphibian and mammalian atrial tissue contain a choline ester which is almost certainly acetylcholine (61, 127, 381), chemical identification has not been carried out, as it has for acetylcholine extracted from the spleen (89), intestine (61), and brain (331) (see also 13). Mammalian atrial tissue also contains both true and pseudocholinesterase (47, 289). This tissue can synthesize appreciable amounts of acetylcholine (32, 45, 62, 90, 349). In the presence of physostigmine or di*iso*propyl phosphorofluoridate (DFP) the spontaneous release of acetylcholine can be detected by the changes which are induced in the membrane conductance and resting and action potentials (349). All these changes are blocked by atropine. It is not known, however, whether the synthesis is confined to nerve endings, and it is of interest that Burn and his co-workers (50) proposed that the pacemaker is under the control of acetylcholine which is produced continuously, and which does not originate from presynaptic endings (53). This concept is based on the ability of acetylcholine to "excite" excised atria when the spontaneous beats have ceased, either after prolonged isolation (52) or by cooling (275). However, it is probable that this effect of acetylcholine is associated with a repolarization of muscle and pacemaker tissue, the spike mechanisms of which have been inactivated by depolarization (347).

2. Autonomic ganglia. Although the evidence for synaptic inhibition in various autonomic ganglia is confusing, and an effective inhibitory action of presynaptic impulses has not been established (98, 183, 198, 246), the administration of adrenaline and noradrenaline to many types of sympathetic and parasympathetic ganglia produces a reversible depression of the postganglionic spike response (40, 44, 118, 170, 206, 207, 210, 247, 261, 263, 264, 273, 277, 291, 294, 350, 351). In some cases lower doses of these substances appear to potentiate transmission through ganglia (40, 44, 210, 261, 350) and it is probable that the variations in the effects obtained depend somewhat on the preparation used, the presence of anaesthetic agents, and the dose of catecholamines administered. Adrenaline has been observed to hyperpolarize ganglion cells (247), but this change in potential is not always present when transmission is depressed by adrenaline. Dihydroergotamine (247) and Dibenamine (118) reduce the depressant effect of adrenaline but Dibenzyline has no such action (277). Paton and Thompson (294) suggested

that adrenaline has a dual action upon neurones of the superior cervical ganglion of the cat, reducing the amount of acetylcholine released from presynaptic terminals as well as depressing its postsynaptic action.

When sufficient tubocurarine or dihydro-β-erythroidine is administered to block the excitatory response to preganglionic stimulation, a slow positive (P) and a late negative potential are recorded from the postganglionic nerve trunks of the isolated superior cervical ganglia of the rabbit and turtle (116, 225). This P wave is increased in amplitude after a brief preganglionic tetanus (116, 118) and is intensified and prolonged by anticholinesterases (116). It is diminished by Dibenamine (118) and reserpine (229), but not by ergotamine, dihydroergotamine or 1-(3,4-dichlorophenyl)-2-isopropylaminoethanol (DCI) (118). It should be noted that 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol (isoproterenol) has a facilitating and not a depressant action upon ganglionic transmission (277).

Eccles and Libet (118) have proposed that the P wave of the rabbit superior cervical ganglion is produced by a hyperpolarization of the ganglion cells, which is the result of the synaptic action of adrenaline released from chromaffin cells within the ganglion by preganglionic cholinergic fibres. It is significant that an adrenaline-like substance has been detected in the venous effluent of the superior cervical ganglion of the cat (40, 232). As yet intracellular recording has failed to reveal the presence of a hyperpolarization corresponding to the P wave, but it is possible that not all ganglion cells generate this potential (117). Nevertheless, further investigation is necessary to establish that the P wave is in fact a postsynaptic potential generated by a permeability change in the ganglion membrane under the influence of adrenaline. It is conceivable that the actions of the catecholamines on transmission within ganglia are of metabolic origin (42, 261). Further evidence for an inhibitory process in rat sympathetic ganglia has been provided by Dempsher *et al.* (92), who have investigated the spontaneous discharges originating in superior cervical ganglia infected with pseudorabies virus. It was suggested that the inhibitory action is exerted on presynaptic terminals of the preganglionic cholinergic fibres.

3. Smooth muscle. When used in reference to smooth muscle, the term inhibition usually means a reduction in muscle tone, and classically the diminution of intestinal movements produced by adrenaline and related amines (359) has been termed an inhibitory process. Bacq and Monnier (12) found that the inhibitory effects of sympathetic nerve stimulation and of adrenaline upon smooth muscle of the feline uterus and bladder were accompanied by an increase in the demarcation potential. Subsequently adrenaline was shown to hyperpolarize the smooth muscle of guinea pig *taenia coli* (40). However, the catecholamines also have excitatory actions upon smooth muscle (137, 359) and recent investigations (9, 10) have indicated that adrenaline, noradrenaline, and isopropylnoradrenaline (42) have a dual effect upon such tissue. Thus on the smooth muscle of the guinea pig *taenia coli*, adrenaline has a direct, presumably synaptic, depolarizing action, which is normally masked by an inhibitory hyperpolarizing effect. This latter effect is considered to be of metabolic origin, and the available evidence points to a control by adrenaline of energy processes concerned with the main-

tenance of the resting potential (9). It is not known to what extent these two actions of adrenaline upon smooth muscle are related to the various types of receptors which have been proposed (see 155). The "classical" adrenergic blocking agents are not very specific antagonists of the inhibition of intestinal smooth muscle by adrenaline (see 288), but the antagonism exhibited by DCI towards many of the inhibitory effects of the catecholamines (163, 303) suggests that β receptors are involved in the inhibitory process.

Bülbring (42) has extended these findings to other tissues, and it is possible that many of the depressant or inhibitory effects of catecholamines are related to a metabolic action which influences the electrical activity and excitability of the cells (see also 126, 248). This concept of a metabolic control of cell activity is of considerable importance, and helps to explain many of the confusing observations that have been made upon various types of smooth muscle (42, 137, 359). In part, the proposed dual action of adrenaline accounts for some of the observations that led to the postulate of excitatory and inhibitory sympathins (314) and that are not readily explicable by a difference between the actions of adrenaline and noradrenaline (362).

For an account of the effect of chemical agents on the inhibition of vascular smooth muscle the reader is referred to a recent review by Furchgott (154).

B. Invertebrate

1. Heart. Recent reviews (151, 213) deal with the pharmacology of the inhibition of molluscan hearts. Many problems remain unsolved, including the synaptic mechanisms which are involved. Acetylcholine and cholinesterase are present in the hearts of many species and usually acetylcholine is a potent inhibitor of the molluscan heart (144). The high sensitivity of the heart of *Venus mercenaria* has led to the use of this preparation for assay purposes (371), and it is probable that in this species the cardioinhibitory transmitter is acetylcholine. Thus, during inhibition produced by stimulation of the visceral ganglion, a substance is produced which has the same effect upon another isolated heart as acetylcholine (304, 370). Physostigmine prolongs the effects of both acetylcholine and nervous inhibition (304), and benzoquinonium blocks the effects of acetylcholine or stimulating inhibitory nerves (151). Welsh and Taub (371, 372) have studied the effect of a variety of choline and betaine esters on this preparation, and concluded that the action of acetylcholine is of the "nicotinic" type. Atropine and tubocurarine are not antagonists of acetylcholine in this preparation (304, 372).

Investigations upon the inhibition of hearts of other molluscs are not as complete, but there is evidence that, whereas acetylcholine inhibits the heart of some lamellibranchs (151), it has an excitant action upon the heart of others (200, 301).

Florey (140) has shown that the heart of the lobster *Palinarus argus* is inhibited by Factor I, extracted from mammalian brain (139), and by an unknown substance present in lobster legs and crustacean central nervous systems. Factor I and acetylcholine both inhibit the hearts of the cephalopods, *Sepiatheuthis sepiodis* and *Octopus vulgaris*. On the other hand the heart of the crayfish *Cam-*

barus clarkii is inhibited by Factor I (139) but is excited by acetylcholine (376). The heart of the crayfish *Astacus trowbridgii* is inhibited by GABA (10^{-5} M), and picrotoxin blocks both the effect of GABA and the cardiac inhibition produced by stimulating the inhibitory nerve (141). Strychnine and atropine are without action. The perfusate from the crayfish heart, collected during stimulation of the inhibitory nerve, contains an inhibitory substance which depresses other hearts. This substance is blocked by picrotoxin and is assumed to be Factor I (141). Brockman and Burson (34) reported briefly that the heart of the crayfish *Cambarus virilis* is depressed by glutamic acid. Maynard (279) has discussed cardiac inhibition in decapod crustacea. γ-Aminobutyric acid mimics the action of the inhibitor fibres to the isolated cardiac ganglion of the lobster *Homarus americanus* (278).

2. Crustacean neuromuscular junction. Three types of inhibition have been observed in crustacean muscle, and all presumably are related to the release of a chemical transmitter from inhibitory nerve terminals. Usually inhibitory nerves terminate near motor nerve endings (354) and under favourable circumstances inhibitory and excitatory nerves can be stimulated separately (133, 156, 175, 186, 187, 222, 262).

α-Inhibition (204, 222) or supplemented inhibition (262) is indicated by a reduction in the amplitude of excitatory junctional potentials (e.j.p.). The reduction depends on the time relationships between inhibitory and excitatory volleys, and is associated with an increased conductance of the postsynaptic membrane (17, 96, 133, 175, 219). Inhibitory volleys may or may not produce an alteration in membrane potential (133, 148, 175, 186, 219); and it is probable that the conductance change produced by the inhibitory transmitter is due to an increase in membrane permeability to chloride ions [*Astacus fluviatilis* (17, 132); *Homarus americanus* (174, 175, 373)]. Fatt and Katz (133) have considered that the change of conductance produced by inhibitory synaptic action in crabs (*Eurapargurus bernhardus* and *Carcinus maenas*) is insufficient to account for the observed decrease in the size of the e.j.p.'s. They proposed that the excitatory transmitters interact with a common postsynaptic receptor, the inhibitory transmitter not only producing a change of conductance but also competing with the excitatory transmitter for receptor sites (see also 131, 204, 222).

β-Inhibition (204, 222) or simple inhibition (262) refers to a direct interference by the inhibitory process with the coupling between synaptic excitation and mechanical contraction. It is demonstrated when inhibition of contraction occurs in the absence of α-inhibition, and is regarded by Marmont and Wiersma as the more important aspect of peripheral inhibition (148, 187, 262).

The third form of inhibition, observed in the crayfish *Orconectes virilis*, has been called presynaptic inhibition, since inhibitory impulses appear to diminish the size of e.j.p.'s by reducing the number of quanta of excitatory transmitter released by excitatory impulses (96). Dudel and Kuffler proposed that this form of inhibition is chemical, and that the substance released from inhibitory nerve terminals increases the ionic conductance both of the postsynaptic membrane, and of the membrane of the excitatory terminals.

Pharmacological investigations of these crustacean inhibitions have been extensive, and, although it is assumed that the same transmitter produces these three types of inhibition in any one species, definite evidence is lacking. The inhibition of the opener of the claw in the crayfish (*Cambarus clarkii*) is not affected by choline, acetylcholine, acetyl-β-methylcholine, adrenaline, nicotine, tubocurarine, muscarine, pilocarpine, strychnine, or caffeine (125), and the inhibitory process is therefore unlikely to be cholinergic. Similarly, peripheral inhibition in the lobster (*Homarus americanus*) is unaffected by acetylcholine, physostigmine, neostigmine, decamethonium, hexamethonium, tubocurarine, or strychnine (175).

Conflicting results have been obtained with GABA and related amino acids. In many cases inhibition is revealed merely by a depression of the contraction evoked by excitatory nerve stimulation, and it is difficult in some cases to determine from the reports the exact mode of action of the substances. γ-Aminobutyric acid depresses the contraction of muscle in the crayfish *Cambarus virilis*, and the crab *Gecarcinus* (34, 251). γ-Amino-β-hydroxybutyric acid has a similar effect (251). Hoyle and Wiersma (186) were unable to demonstrate an inhibitory action of GABA on a series of crayfish and crab muscles. In the crayfish *Astacus fluviatilis* the action of GABA (10^{-4} M) is similar to that of the inhibitory transmitter (17), as is also the case in the lobster *Homarus americanus* (175). In the lobster, GABA (10^{-11} to 10^{-3} M) reversibly reduces both the inhibitory and excitatory junctional potentials and increases membrane conductance. The associated change in membrane potential is similar in direction to that produced by inhibitory impulses (175) and it has been concluded that GABA activates inhibitory synapses on lobster muscle fibres. Related amino acids, β-alanine, γ-amino-β-hydroxybutyric acid, γ-aminocrotonic acid, and guanidinoacetic acid, have similar effects, whereas the long-chain ω-amino acids are inactive. The contraction of the opener of the claw of the crayfish *Cambarus clarkii* is depressed by amino acids closely related to GABA (312), and the structural requirements for this inhibition are highly specific. The most potent amino acid is GABA and activity is reduced sharply when the carbon chain is either increased or reduced in length. In this preparation GABA inhibits the contraction produced by excitatory nerve stimulation (353) and by L-glutamic acid (312); it also reduces the magnitude of e.j.p.'s and increases the membrane conductance (353). This amino acid thus mimics the effect of the inhibitory transmitter, but, as with the lobster (175), the equilibrium potentials for inhibitory action and for the amino acid-induced potential alteration have not been compared. Van der Kloot (352) has presented evidence that GABA also causes the release of an inhibitory transmitter in the crayfish. In the crab *Cancer magister*, the effect of GABA differs from that of the inhibitory transmitter (148), and the amino acid possibly reduces excitatory transmitter action either by competing for receptor sites or by reducing the quantity of transmitter released. GABA has a dual effect at the neuromuscular junction of the crayfish *Orconectes virilis* (96). It produces an increase in the postsynaptic membrane conductance, and the equilibrium potential for the associated alteration in membrane potential is identical

with that of the inhibitory junctional potential (219). Guanidinoacetic acid has a similar but weaker effect. γ-Aminobutyric acid also has an effect upon the release of excitatory transmitter from the terminals of the motor nerve (96) and thus mimics presynaptic inhibition.

In view of the possible function of GABA as a crustacean inhibitory transmitter, attempts have been made to extract this compound from nerve fibres. Although it has been reported (146) that the peripheral nervous tissue of the crab *Cancer magister* and the lobster *Homarus americanus* contains no detectable GABA but yields Substance I, which has a GABA-like action on crustacean stretch receptors (142, 145, 146) and crustacean muscle (144), GABA has recently been detected in the nervous system of the lobster *Homarus americanus* (212a). There is considerably more of this amino acid in the peripheral inhibitory nerve fibres than in motor fibres. Furthermore, GABA has been extracted from muscle and nerve of the crab *Cancer borealis*, together with β-alanine, taurine, proline, and an unidentified substance (212). It is of interest that Florey and Hoyle (148) considered that the action of GABA differs from that of the inhibitory transmitter of *Cancer magister*, whereas the effect of GABA in *Cancer borealis* appears to be similar to that of the inhibitory process (212).

Picrotoxin is a convulsant when administered to crustacea (138), and appears to be a specific depressant of synaptic inhibition in many crustacean neuromuscular preparations. Picrotoxin reversibly reduces the effect of inhibitory nerve stimulation in the crayfish *Orconectes immunis*, but has no action upon synaptic excitation (313). A similar action is observed in *Cambarus clarkii*, *Cambarus virilis* (312, 353) and *Orconectes virilis* (219). In all of these preparations picrotoxin also blocks the action of GABA, but has no effect upon excitatory junctional potentials or the resting membrane conductance. It has been proposed that picrotoxin has a postsynaptic action, preventing the access both of the inhibitory transmitter and of GABA to the inhibitory receptor sites (313). If this be so, the proposal by Fatt and Katz (133) that excitatory and inhibitory transmitters compete for a common receptor site cannot be correct and it is possible that their results are explicable by presynaptic inhibition. In the lobster *Homarus americanus*, picrotoxin blocks the action of both the inhibitory transmitter and GABA (175), and is presumed to inactivate inhibitory synapses, since excitatory junctional potentials and the membrane resting potential remain unaltered. On the other hand, although picrotoxin prevents inhibition of the mechanical contraction in the crab *Cancer magister* (148), it also reduces the size of excitatory junctional potentials and does not antagonize the action of GABA.

Factor I, extracted from mammalian central nervous tissue (139), has an inhibitory effect upon muscle in the crayfish *Cambarus clarkii* (139) and *Cambarus virilis* (34, 251), and the crab (139, 251).

3. Crustacean stretch receptor. The physiology and pharmacology of the crustacean stretch receptor have been reviewed in detail in several publications (119, 130, 218, 219). These receptors, from a variety of crayfish, lobsters, and crabs, have an inhibitory nerve supply, stimulation of which depresses the frequency of the sensory discharge evoked by stretch deformation of the organ (48, 221).

The inhibitory action is confined to the dendrites and is produced by an increase in membrane conductance (221), there being an increase in membrane permeability to potassium (120, 220) and chloride ions (178, 221). The associated alterations in the postsynaptic membrane potential depend upon the resting potential level of the cell, and the equilibrium potential for the ionic movements varies in different preparations (120, 178, 220, 221).

There have been extensive pharmacological studies upon the stretch receptor, particularly with amino acids related to GABA. This amino acid has little or no effect upon sensory nerves or stretch receptor axons, but concentrations of 10^{-4} to 10^{-5} M produce a conductance change in the membrane of the stretch receptor, which closely resembles that produced by synaptic inhibitory action (121, 178, 220). There is exactly the same equilibrium potential for the inhibitory postsynaptic potential and for changes in membrane potential produced by GABA. It is probable that GABA action is confined to the dendrites and the cell body of the receptor (220), but a site of action restricted to inhibitory subsynaptic areas is rendered unlikely by the finding that stretch receptor cells reported to be devoid of inhibitory synapses (3) are also sensitive to GABA (220). An important observation is that picrotoxin diminishes both neural and GABA inhibitory action (219). Strychnine does not block the inhibitory synaptic process (365).

The inhibitory actions of a large series of ω-amino and guanidino acids structurally related to GABA have been investigated (14, 121, 178, 250), and the action of those substances found to be depressants appears to be identical with that of GABA. GABA was found to be the most potent amino acid, and decreasing or increasing the chain length by one carbon atom (β-alanine or δ-amino-*n*-valeric acid) markedly reduced activity. Several guanidino acids, particularly guanidinoacetic and β-guanidinopropionic, were also quite potent (119, 121). Two interesting processes have been observed when amino acids are administered to the solution bathing stretch receptors (119, 220): the transient action of GABA is restored by stirring the solution; with other depressants the transient actions are not restored by stirring. It has been suggested (119, 220) that GABA, and possibly some of the closely related amino acids are removed from the solution in the close vicinity of the receptor sites, either by enzymic alteration or by uptake into the cell. On the other hand those depressions not restored by stirring have been attributed to a desensitization which probably is similar to the process of the same name which has been observed at the neuromuscular junction (345).

Factor I (139) depresses the response of these receptors to stretch (14, 124, 139, 251) and to acetylcholine (379). The preparation can be used as an assay for Factor I (124), and, although GABA might be responsible for some of the activity (14), this amino acid is not necessarily always a component of Factor I (252, 253). In addition, Substance I isolated from crustacean nervous tissue (145, 146) inhibits the stretch receptor but contains no detectable GABA. Picrotoxin prevents the action of Factor I and Substance I (124, 146, 250).

Although Elliott and Florey (124) reported that L-adrenaline bitartrate and

L-noradrenaline bitartrate were inactive on stretch receptor neurones of *Cambarus virilis* in concentrations of approximately 3×10^{-3} M, it has been reported recently (250) that the catecholamines, 3-hydroxytyramine, D-noradrenaline, L-noradrenaline and L-adrenaline, have appreciable depressant activity upon the receptors of the crayfish *Pacifastacus leniusculus*. 3-Hydroxytyramine was found to be about one hundred times more potent than GABA on this preparation, and a pharmacological analysis indicated that GABA and the catecholamines do not combine with the same membrane receptor sites. In particular, picrotoxin was not a very effective antagonist of 3-hydroxytyramine, but chlorpromazine and Dibenzyline almost completely blocked the action of the amine, though they were ineffective against GABA. The site of action of these agents remains to be elucidated.

γ-Aminobutyrylcholine depresses responses of stretch receptors but less effectively than GABA (178, 250); other choline esters, including butyrylcholine and acetylcholine are excitants of the cell (178, 379).

Caution has been expressed toward assuming that GABA is the naturally occurring inhibitory transmitter of crustacean stretch receptors (119, 121, 220). Although the postsynaptic action of GABA appears to be identical to that of the transmitter, and the actions of both substances are blocked by picrotoxin, the action of GABA is not confined to inhibitory subsynaptic areas. Furthermore, crustacean nerve extracts contain inhibitory factors which, although as yet not fully characterized, differ from GABA (122, 142, 146).

IV. CONCLUSIONS

The principal aim of pharmacological studies upon chemical inhibitory processes is the elucidation of the nature of transmitter agents. Before a given compound can be fully identified as the inhibitory transmitter operating at a particular synaptic region, it must satisfy all of the following requirements (73, 293): the conductance change induced in the inhibitory subsynaptic membrane must be identical with that of the natural transmitter; the substance must be present or synthesized in the appropriate synaptic terminals and released by stimulation of the inhibitory nerve fibres; the interactions of the compound with blocking and potentiating agents must be identical with those of the transmitter. When examined in the light of these requirements very few substances qualify as proven transmitters. In particular, it is difficult to satisfy the criterion that the substance be located in and released from inhibitory nerve terminals, and it is usually sufficient to demonstrate that the substance can be extracted from the tissue and is released by inhibitory nerve stimulation. Future investigations of this nature will be aided by several comparatively recent techniques. These include the histochemical localization within tissues of particular compounds; the technique of separating subcellular particles, especially nerve endings (94, 375); and the ability to determine quantitatively enzymes of single neurones (169) which may be associated with the manufacture and inactivation of transmitters.

At the present time it is generally accepted that acetylcholine is the cardiac vagal inhibitory transmitter in mammals and amphibia. However, no other

vertebrate inhibitory transmitter has been identified, and none of the substances which have been proposed as transmitters satisfies the requirements discussed above. The only positive finding with respect to postsynaptic inhibition in mammals and amphibia is the specific blocking action of tetanus toxin, strychnine, and closely related compounds. Presynaptic inhibition in the mammalian spinal cord, which is resistant to strychnine, appears to be diminished by picrotoxin, which does not diminish postsynaptic inhibition. It is unknown to what extent this action of picrotoxin explains its stimulant effect upon the central nervous system.

Studies upon invertebrate inhibition indicate the strong possibility that acetylcholine is an inhibitory transmitter in *Aplysia depilans*, but the transmitters for the inhibition of crustacean stretch receptors and at the crustacean neuromuscular junction remain unknown. At both of these latter sites the blocking action of picrotoxin appears to be specific.

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