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Pharmacology of the Second Messenger, Cyclic Guanosine 3′,5′-Monophosphate, in the Cerebellum

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I. Introduction

THE cyclic nucleotide cGMP† has been demonstrated to be an intracellular second messenger system within the cerebellum. High concentrations of cGMP (Chan-Palay and Palay, 1979; Rubin and Ferrendelli, 1977; Steiner et al., 1972; de Vente et al., 1989; Waldman and Murad, 1987), of the synthetic enzyme, guanylate cyclase (Ariano et al., 1982; Waldman and Murad, 1987; Zwiller et al., 1981), of the degradative enzyme cGMP phosphodiesterase (Greenberg et al., 1978; Uzunov and Weiss, 1972), and of cGMP-dependent protein kinases (Schlichter et al., 1980) have been found to be present in the cerebellum. Additionally, there have been a large number of pharmacological analyses of drug effects both on cerebellar cGMP levels and on the associated enzymic machinery of this second messenger. It is the purpose of this review to critically assess our current interpretations of where this cGMP is generated and to examine the transducer mechanisms that are coupled to cGMP formation. The neurochemical anatomy of the cerebellar circuits and their afferents also will be reviewed when relevant to an understanding of the effects of drugs on cerebellar cGMP levels.

II. Methodology

A. Microwave Tissue Fixation

For rapid stabilization of postmortem changes in cGMP levels, immersion in liquid nitrogen (Kimura et al., 1974) or "nitrogen brain blowing" (Guidotti et al., 1974) were first used. However, these methods make fine dissection of brain regions difficult or impossible. Subsequently, a number of laboratories demonstrated the ease and utility of focused microwave fixation for the determination of cerebellar cGMP levels (Dodson et al., 1979; Guidotti et al, 1975; Jones and Stavinoha, 1977; Mao et al., 1974b; Wood et al., 1982). In many laboratories, this method of tissue fixation is highly amenable to subsequent microdissection of brain regions and yields basal cGMP levels in the range of 1–3 pmol/mg protein.

B. Tissue Microdissection

Microdissection of the cerebellum involved dissection of the cortex, vermis and deep cerebellar nuclei (Biggio et al., 1977a; Guidotti et al., 1975; Rubin and Ferrendelli, 1977). Of the drugs tested to date, parallel changes in cGMP levels occurred in all 3 regions, except in the case of muscarinic agonist administration, which increased only vermal cGMP levels (Rubin and Ferrendelli, 1977). Further microdissection of cell layers in the cerebellum indicated that generally 80% of the changes in cGMP levels occurs in the molecular layer and 20% in the granular layer (Rubin and Ferrendelli, 1977). However, not all drug effects have been monitored in such anatomical detail, indicating that this may not always be the case.

C. Routes of Drug Administration

The in vivo evaluation of drug effects on cerebellar cGMP is most often determined with parenteral drug administration. However, when drug bioavailability is an issue or when the site(s) of drug action is being studied, then direct intracranial injections are performed. These routes include intraventricular (Danysz et al., 1989; McCaslin and Morgan, 1986b), intracisternal (Wood et al, 1982), and direct intracerebellar (Rao et al., 1990b,c; Wood et al., 1987, 1988b, 1989a,d, 1990a) injections. Drug injections into extracerebellar brain regions, from which afferent pathways originate, have also been used to define drug effects on cerebellar inputs (section V.B.1).

D. Lesions/Mutant Mice

The relative roles of afferent fiber pathways as well as Purkinje and granule cell populations in cGMP responses to drug treatments have been investigated by the use of both chemical lesions and genetically mutant mice. In the case of the climbing fiber system (section IV), efficient lesions can be obtained with the toxin 3-acetylpyridine (Guidotti et al., 1975; McBride et al., 1978). However, although this lesion is easily created in rats, in our hands, this toxin is not useful in mice because it is extremely lethal.

For the selective depletion of cell populations, virus-induced granule cell loss in the hamster cerebellum was reported (Young et al., 1974). For mice, a number of strains are available with selective losses of granule ("Weaver mouse") and Purkinje ("Nervous mouse") cells (table 1).

E. Confounding Variables

1. Motor activity. The issue has been raised that many drug effects on cerebellar cGMP may result from changes in the motor state of an animal. The basis for this hypothesis was the observation of elevated cerebellar

†Abbreviations: cGMP, cyclic guanosine 3′,5′-monophosphate; NMDA, N-methyl-D-aspartate; TRH, thyrotropin-releasing hormone; GABA, γ-aminobutyric acid; EAA, excitatory amino acid; NO, nitric oxide; PCP, phencyclidine; CNS, central nervous system; CCK, cholecystokinin; DN-1417, γ-butyrolactone-γ-carbonyl-L-histidyl-L-proline amide citrate; CPP, 3(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid.

TABLE 1
Characteristics of the Nervous and Weaver neurologically mutant mice strains

Parameter	Nervous mouse	Weaver mouse	Reference
Lesion	Purkinje cell loss (80–90%)	Granule cell loss (80%)	McBride et al., 1976
Adenosine A_1 receptors	Normal	Decreased	Goodman and Snyder, 1982 Wojcik and Neff, 1983
GABA-A receptors		Decreased	East and Dutton, 1981
GABA-B receptors		Decreased	Wojcik et al., 1985
Glutamate levels	Normal	Decreased	Hudson et al., 1976 McBride et al., 1976 Roffer-Tarlov and Sidman, 1978
cGMP levels	Decreased		Mao et al., 1975b Schmidt and Nadi, 1977
Guanylate cyclase	Normal		Schmidt and Nadi, 1977

cGMP levels in the cerebella of rats trained to run in an activity wheel (Meyerhoff et al., 1979). Similarly, rats trained to swim a 2.5-m course possessed elevated cerebellar cGMP levels; this effect was blocked by competitive NMDA (section III.A) antagonists (McCaslin and Morgan, 1986a–c). Pharmacological studies using motor stimulants also have demonstrated a role for an enhanced motor activity in the increases in cerebellar cGMP induced by both apomorphine and TRH (section V.B.3) but not by harmaline (Lundberg et al., 1979). In these studies, the effects of TRH and apomorphine were significantly attenuated, but not absent, in rats paralyzed with *d*-tubocurarine and mechanically ventilated (Lundberg et al., 1979). In paralyzed animals, the decreases in cGMP induced by the depressants pentobarbital, halothane, and ethanol were also reduced (section III.B.5).

Thus, it appears that enhanced motor activity can result in increased cerebellar cGMP levels and vice versa. However, these parameters are not strictly correlated: the recovery of locomotor activity after pentobarbital treatment is 30–60 min, whereas the recovery of cerebellar cGMP levels is 120–150 min (Morgan and Pfeil, 1984; section III.B.5); genetically dystonic rats which have normal motor activity patterns possess cerebellar cGMP levels that are 33% of that of control rats (Lorden et al., 1985); whereas C57Bl/6J mice have concomitant increases in motor activity and cerebellar cGMP levels after morphine treatment and DBA mice have decreased cerebellar cGMP in the absence of changes in motor activity (Racagni et al., 1979; section V.B.5); cerebellar cGMP is not increased by all agents that potentiate dopaminergic transmission and increase motor activity (Breese et al., 1979a; section V.B.1; table 2).

TABLE 2
Lack of correlation of changes in motor activity and cerebellar cGMP after treatment with dopaminergics (Breese et al., 1979a)

Drug	Locomotor activity (-fold of control)	Cerebellar cGMP (-fold of control)
Amantadine	3.3*	1.25*
Piribedil	4.1*	0.73
Lergotrile	4.7*	0.97
Apomorphine	8.4*	3.13*
d-Amphetamine	10.4*	3.52*
Methylphenidate	10.7*	3.18*

* $p < 0.05$.

2. Stress. A further complication in the analysis of drug and behavioral effects on cerebellar cGMP levels is the potential for a significant stress component in any experimental paradigm. Indeed, elevated cerebellar cGMP levels have been measured in fighting mice (Dinnendahl, 1975), in mice stressed in ice water or on a hot plate (Dinnendahl, 1975), and in rats maintained at 4°C (Mao et al., 1974a). In all cases, these elevations in cGMP returned to normal between 15 and 30 min after cessation of acute or chronic stress exposure.

The pharmacology of stress-induced cGMP increases also has been investigated (Dinnendahl and Gumulka, 1977). These increases are blocked by pretreatment with pentobarbital, diazepam, chlorpromazine, haloperidol, aminooxyacetic acid, reserpine, clonidine, and high doses of propranolol (no stereospecificity). In contrast, acute stress effects on cGMP were not altered by pretreatment with phentolamine, atropine, diphenhydramine, cyproheptadine, or indomethacin (Dinnendahl and Gumulka, 1977). These data lead to the conclusion that dopaminergic and GABAergic pathways are involved in stress-induced increases in cerebellar cGMP (Wood et al., 1984a), whereas noradrenergic, serotonergic, histaminergic, and cholinergic pathways are not. Additionally, enhanced prostaglandin synthesis is not a component of the cascade leading to increased cGMP.

The role of dopaminergic and GABAergic pathways in stress-induced cerebellar cGMP increases is further reflected by studies of rats habituated to handling (Corda et al., 1980). In these animals, the basal cerebellar cGMP levels were 30% of naive rats and could not be further decreased by the dopamine antagonist haloperidol (section V.B.1) or the GABAergics diazepam and muscimol (section III.B.1). In contrast, apomorphine (section V.B.1) still increased cerebellar cGMP in these animals habituated to handling (Corda et al., 1980).

3. Respiratory depression. It has been demonstrated in rats paralyzed with *d*-tubocurarine and mechanically

ventilated that cerebellar cGMP levels are inversely related to arterial carbon dioxide tension (Mueller et al., 1979). Therefore, investigators who observe decreases in cerebellar cGMP levels with drugs that induce respiratory depression should interpret their data with some caution.

F. In Vitro Studies

The study of cerebellar cGMP levels in vivo offers the potential to determine drug effects on cerebellar afferent pathways, to examine drug effects in the presence of in vivo neuronal firing patterns, and to determine drug bioavailability. However, when the purpose of a study is to define mechanism(s) and site(s) of action of a drug, investigators often integrate such in vivo studies with in vitro evaluations in which experimental variables can be more easily regulated.

1. Cerebellar slices. Studies of tissue slices obtained from immature rat brain have demonstrated that cerebellar slices generate the greatest concentration of cGMP, paralleling in vivo observations (Palmer and Duszynski, 1975). The higher levels of cGMP in this brain region appear to result from lower levels of cGMP phosphodiesterase in the cerebellum (Greenberg et al., 1978).

A number of investigators have investigated the actions of EAA agonists (section III.B.6) on cGMP generation in cerebellar slices (Garthwaite and Brodbelt, 1989; Garthwaite, 1982; Schmidt and Nadi, 1977; Schmidt et al., 1977). These studies demonstrated positive modulation by kainate; however, the buffers used in these studies all contained Mg^{2+}, an antagonist of the NMDA receptor complex (Ascher et al., 1988). As a result, modulation of cGMP by NMDA was only weakly demonstrated or not demonstrated, whereas, indeed, there is such modulation in vivo (III.B.6). Using a number of chemical lesions of cell types in these slices, investigators concluded that the major cells initiating cGMP accumulation include the granule cells and astrocytes but not Purkinje cells (Garthwaite and Brodbelt, 1989; Garthwaite, 1982); these findings are in agreement with immunohistochemical studies (section III.A).

2. Cell fractions. Freshly isolated bulk cell fractions obtained from immature rat cerebellum (Gordon and Balazs, 1983) have shown a rank order for guanylate cyclase activity as follows (Bunn et al., 1986; Garthwaite and Garthwaite, 1987): glomerulus particles (mossy terminals + Golgi terminals + granule dendritic digits) > astrocytes > Purkinje cells. Guanylate cyclase was activated more than 10-fold in all cell fractions by the NO prodrug, sodium nitroprusside.

3. Cultured neurons. Cultures composed of >90% granule cells can be obtained from a culture of immature rat cerebellum (Drejer and Schousboe, 1989). These neurons are EAA utilizing in that they demonstrate Ca^{2+}-dependent glutamate release (Gallo et al., 1982; Levi et al., 1984). Studies of EAA modulation of cultured granule cells have shown NMDA- and kainate-dependent increases in cGMP, with concomitant increases in Ca^{2+} uptake (Favaron et al., 1988; Novelli et al., 1987; Novelli and Henneberry, 1987; Wrobleweski et al., 1987). The actions of NMDA also were antagonized by Mg^{2+}, competitive NMDA antagonists, and PCP agonists and were modulated by allosteric glycine receptor agonists (Wrobleweski et al., 1989). In cerebellar granule cell cultures, sodium nitroprusside stimulates guanylate cyclase and augments cGMP levels (Novelli et al., 1987; Novelli and Henneberry, 1987). NMDA-dependent c-*fos* expression has been shown to occur in the cascade of information transfer to the nucleus of these cells (Szekely et al., 1989). In toto, these data are consistent with the presence of both NMDA and kainate EAA receptors on granule cells. Cultured granule cells also possess functional GABA-A receptors (Meier et al., 1984; Vaccarino et al., 1987) and show NMDA-dependent increases in metabolism of inositol phospholipids (Nicoletti et al., 1987).

III. Intracerebellar Systems

A. Excitatory Amino Acid and GABAergic Pathways

The cerebellum is a unique CNS area for biochemical studies in that a large number of the neuronal participants in the afferent, efferent, and endogenous circuitry are chemically characterized. Indeed, the only output neuron of the cerebellum, the Purkinje cell (fig. 1), is known to be GABAergic (Palay and Chan-Palay, 1974). Similarly, the inhibitory interneurons (fig. 1) of the molecular layer (basket cells and stellate cells) and the

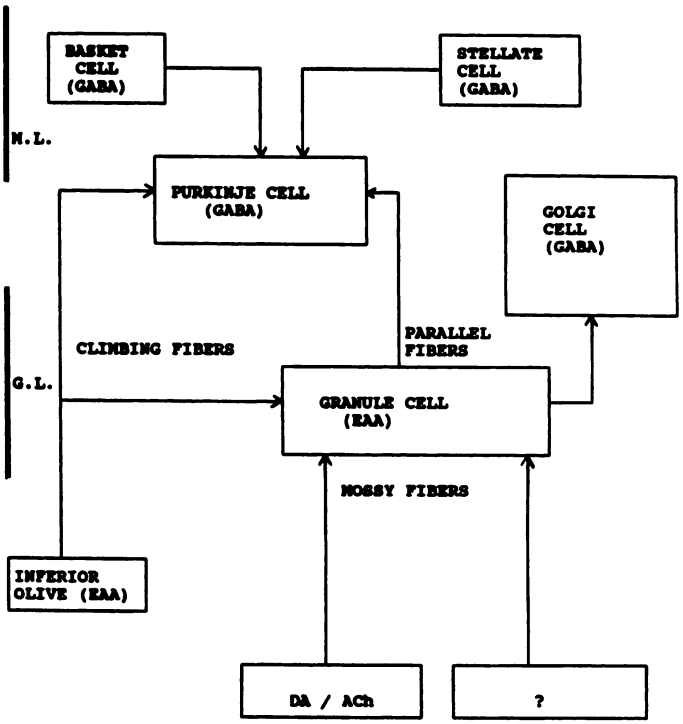

FIG. 1. Basic circuitry diagram of the cerebellum with the neurons of the molecular (M.L.) and granular (G.L.) cell layers. DA, dopamine; ACh , acetylcholine.

granule cell layer (Golgi cells) are all GABAergic (Palay and Chan-Palay, 1974). The granule cell population of the granular layer of the cerebellum utilizes an EAA as its transmitter (Drejer et al., 1983; Young et al., 1974), as do the climbing fibers that derive from neurons in the inferior olive (McBride et al., 1978; Nadi et al., 1977; Roffer-Tarlov and Siman, 1978). In contrast, the neurochemical makeup of mossy fiber pathways is less well defined and will be discussed later (section V.A)

Both neurochemical and anatomical data suggest a delicate physiological balance between the EAA and GABAergic pathways within the cerebellum (Lehmann and Wood, 1988; Martin and Wood, 1987; Wood et al., 1988a). Indeed, this suggestion is borne out by a large number of pharmacological studies of cerebellar cGMP levels. However, the site of generation of cGMP within the cerebellum has been a difficult issue to address and has required a number of experimental approaches. Initially, a direct correlation between Purkinje cell firing rates and cerebellar cGMP levels (Biggio et al., 1977b,d; Biggio and Guidotti, 1976; Wood et al., 1982), along with the high levels of guanylate cyclase in Purkinje cells (Ariano et al., 1982), led to the suggestion that cGMP is generated in these cells and that levels of this cyclic nucleotide are a biochemical index of Purkinje cell activity (Biggio et al., 1977b,d). However, subsequent experiments with granule cell cultures demonstrated that cGMP can also be generated in these cell types (McCaslin and Morgan, 1987; Novelli et al., 1987; Novelli and Henneberry, 1987). Studies in which cell fractionation was used supported the generation of cGMP in granule cells but not Purkinje cells (Garthwaite and Garthwaite, 1987). Additionally, the generation of cGMP in glial cells was suggested by these cell fractionation approaches (Garthwaite and Garthwaite, 1987). Such data are consistent with a number of immunohistochemical studies (Chan-Palay and Palay, 1979; Cumming et al., 1979; de Vente et al., 1989) which have demonstrated basal and sodium nitroprusside-dependent increases in cGMP in the Bergmann glia of the Purkinje cell layer, in the Bergmann glial fibers of the molecular layer, and in the astroglia of the granular cell layer. No cGMP was demonstrated in Purkinje cells or granule cells when immunohistochemical techniques were used. Under conditions of nitroprusside stimulation, low levels of cGMP could be demonstrated in fibers in the granule cell layer, which might be mossy fiber inputs (de Vente et al., 1989). These histochemical observations suggest that a component of the increased cGMP levels observed in cerebellar granule cell cultures (section II.F.3), after the addition of EAA receptor agonists, might involve the 2–10% glial cell contamination of such cultures (Drejer and Schousbe, 1989).

Biochemical studies of cerebellar soluble and particulate cell fractions have clearly demonstrated stimulation of guanylate cyclase by sodium nitroprusside, a drug that spontaneously generates NO (Katsuki et al., 1977). These early data suggested that NO can activate cerebellar guanylate cyclase to generate increased cGMP levels in vitro. In efforts to define the locus of cGMP generation and the possible role of NO in cGMP formation, pharmacological experiments both in vitro with cerebellar slices (Bredt and Snyder, 1989; Garthwaite et al., 1988; Garthwaite et al., 1989a,b) and in vivo (Wood et al., 1990b; Wood and Rao, 1990; Wood, 1990) have demonstrated that EAA-dependent increases in cerebellar cGMP are dependent upon the prior formation of NO from arginine via NO synthase. Thus, the NO synthase inhibitor, N-monomethyl-L-arginine, after direct intracerebellar administration, will antagonize increases in cerebellar cGMP elicited by the EAA agonists (section III.B.6) NMDA, kainate, and quisqualate as well as by pharmacologically induced EAA release after harmaline (section IV) or pentylenetetrazol (section III.B.6) treatment (Wood et al., 1990b; Wood and Rao, 1990; Wood, 1990). These data have led to the hypothesis that activation of EAA receptors on granule and Purkinje cells results in the formation of NO, which is a diffusible intercellular communicator entering glial and neuronal cells where it activates guanylate cyclase and augments cGMP formation (Bredt and Synder, 1989; Garthwaite et al., 1988, 1989a,b; Wood et al., 1990b; Wood and Rao, 1990; Wood, 1990). Such a mechanism allows a large amplification, via diffusion of NO to many cells, for a small increase in EAA input to the neurons generating NO and explains the steep dose-response curves for cGMP generation noted with EAA receptor agonists (Wood et al., 1989a)

The anatomical proximity of glial cells and their complex associations with neurons (Hatten et al., 1984; Palay and Chan-Palay, 1974; Reese et al., 1985) also allows rapid entry of NO for activation of glial guanylate cyclase. Indeed, the immunohistochemistry of cGMP in glia demonstrated glial processes around Purkinje cells, around synapses between Purkinje cell thorns and axonal boutons, around mossy fiber rosettes, and around granule cells (Chan-Palay and Palay, 1979). Biochemical studies also have demonstrated an enrichment of guanylate cyclase in freshly isolated cerebellar glial cell fractions (Bunn et al., 1986). This glial enzyme was found to be potently stimulated by sodium nitroprusside. However, the functional role of cGMP as a second messenger in glial cells remains to be defined.

B. Pharmacology

1. γ-Aminobutyric acid-A/benzodiazepine receptor modulators. The GABA-A/benzodiazepine/chloride channel macroreceptor complex consists of a number of protein subunits for which the regional stoichiometries are under intense investigation (Meinecke et al., 1989). However, both receptor autoradiographic and immunohistochemical studies have demonstrated cerebellar GABA-A/benzodiazepine receptor complexes in locations compatible with Purkinje cell dendrites, stellate

and basket cell bodies, and granule cells (Meinecke et al., 1989; Palacios et al., 1980; Richards et al., 1987). Receptor-binding and biochemical studies have also demonstrated the GABA-A/benzodiazepine receptor complex on cultured (section II.F.3) and freshly isolated (Olsen and Mikoshiba, 1978) granule cells. Consistent with these studies, Weaver mice which have a granule cell deficit (table 1) have a 73% loss of GABA-A receptor binding in the cerebellum (Olsen and Mikoshiba, 1978).

In addition to the GABA-A/benzodiazepine sites at which drugs can modulate GABAergic transmission, there are ancillary barbiturate-binding sites on this macromolecular complex that also can lead to allosteric modulation of GABA-A receptor function. In light of the large number of inhibitory GABAergic interneurons within the cerebellum and the availability of a large number of pharmacological agents to manipulate GABAergic transmission, it is not surprising that the most comprehensive reports of the pharmacology of cerebellar cGMP have been concerned with the GABA-A receptor complex (table 3).

It is clear from such studies that the GABA-A agonist, muscimol (Biggio et al., 1977a,d; Mohler et al., 1981), intraventricular GABA itself (Mao et al., 1974b), a large number of benzodiazepine agonists (table 3), the GABA transaminase inhibitor, aminooxyacetic acid (Dinnendahl and Gumulka, 1977), and barbiturates (section III.B.5) all dramatically decrease cerebellar cGMP levels. The actions of diazepam have also been shown to involve decreases in cGMP in both the vermis and the cerebellar hemispheres (Rubin and Ferrendelli, 1977). In the case of the vermis, the proportion of the total decrease in cGMP observed appears to be 70% in the molecular layer and 30% in the granular layer (Rubin and Ferrendelli, 1977).

Local intracerebellar administration of either muscimol or diazepam induced the same degree of cGMP decrease as observed by parenteral drug administration, actions consistent with activation of the cerebellar GABA-A/benzodiazepine receptor complex (Biggio et al., 1977d). Additionally, the actions of parenteral muscimol and diazepam were not altered by 3-acetylpyridine lesions (section IV), indicating a lack of involvement of the climbing fiber system in the actions of these drugs (Biggio et al., 1977d; Biggio and Guidotti, 1976).

The actions of diazepam in decreasing basal cerebellar cGMP were potently blocked by the benzodiazepine receptor antagonist, flumazenil (Mohler et al., 1981), whereas the actions of muscimol and barbiturates were unaltered by this antagonist. These data support the involvement of benzodiazepine receptors in the actions of benzodiazepines, a suggestion previously proposed based on correlations between benzodiazepine receptor affinity and potency to decrease cerebellar cGMP in vivo (Costa et al., 1975). Additionally, the active diazepam metabolites, desmethyldiazepam and chlorodesmethyldiazepam, were also active in decreasing cerebellar cGMP levels (Govoni et al., 1976). The atypical anxiolytic agents, zopiclone, CL 218,872, and CGS 9895, which also decrease cerebellar cGMP levels, were antagonized by flumazenil, indicating that benzodiazepine receptors also mediate their actions (Mohler et al., 1981; Wood et al., 1984b, 1986).

Benzodiazepine inverse agonists have the opposite pharmacological profile in that they increase cerebellar cGMP (Wood et al., 1984c). These include methyl-β-carboline-3-carboxylate (Burkard et al., 1985), ethyl-β-carboline-3-carboxylate (Fujimoto et al., 1982; Koe and Lebel, 1983), and methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (Govoni et al. 1976). The increases in cerebellar cGMP induced by these inverse benzodiazepine agonists are reversed in a dose-dependent fashion by flumazenil, indicating that their actions are mediated by benzodiazepine receptors. At doses which do not alter basal cerebellar cGMP levels, ethyl-β-carboline-3-carboxylate (Fujimoto et al., 1982; Koe and Lebel, 1983) antagonizes the depressant actions of diazepam on cGMP levels.

2. γ-Aminobutyric acid-B receptor agonists. Within the cerebellum, GABA-B receptors have been observed at a number of anatomical loci that can effectively modulate cGMP levels. Lesions with 3-acetylpyridine have demonstrated receptors on climbing fibers (Kato and Fukuda, 1985), studies of mutant mice have demonstrated functionally coupled receptors on granule cells (Wojcik et al., 1985), and autoradiographic studies have revealed receptors on Purkinje cell dendrites and granule cells (Wilkin et al., 1981). Therefore, these inhibitory receptors can directly decrease activity of both Purkinje and granule cells within the cerebellum as well as decrease positive climbing fiber input. Recent autoradiographic studies also have demonstrated a clear topographic GABA-B receptor distribution with parasaggital zones of high and low binding; this distribution correlates with the parasaggital zonation of both afferent and efferent pathways (Albin and Gilman, 1989).

As would be predicted by the GABA-B receptor distribution, baclofen, an agonist at these receptors, dose dependently (Gumulka et al., 1979a) and time dependently (Mailman et al., 1978) decreased cerebellar cGMP levels. Pretreatment with baclofen also was able to antagonize the increases in cerebellar cGMP evoked by the GABAergic antagonists, isoniazid and picrotoxin, but not those evoked by either pentylenetetrazol or arecoline (Gumulka et al., 1979a).

3. Adenosine modulators. Autoradiographic studies were the first to clearly localize A_1 receptors to cerebellar granule cells and to demonstrate a decrease in their numbers in Weaver but not Nervous mice (table 1; Goodman and Snyder, 1982; Goodman et al., 1983). Subsequent biochemical studies with Neurological mutant mice (Wojcik and Neff, 1983) and granule cell

TABLE 3

*Drug effects on cerebellar cGMP in the cerebellum of the rat and mouse**

Drug	Dose (kg)	Route	Time	cGMP (% control)	Rat/ mouse	Reference
			Drugs acting via climbing fiber pathway			
Harmaline	6 mg	ip	15 min	200	R	Biggio et al., 1977c
Harmaline	40 mg	ip	10 min	502	M	Rubin and Ferrendelli, 1977
Harmaline	40 mg	ip	10 min	319	M	Wood et al., 1982
Harmaline	40 mg	ip	10 min	562	R	Costa et al., 1974
Harmaline	40 mg	ip	10 min	551	M	Opmeer et al., 1976
Pargyline	75 mg	ip	10 min	100	R	Costa et al., 1974
Deprenyl	5 mg	ip	10 min	100	R	Costa et al., 1974
3-Acetylpyridine	90 mg	ip	4 days	50	R	Biggio et al., 1977c
			Drugs acting via mossy fiber input			
Monoaminergic agents						
Amphetamine	15 mg	ip	15 min	310	M	Rubin and Ferrendelli, 1977
Amphetamine	15 mg	ip	10 min	215	M	Narumi et al., 1983
Methamphetamine	3 mg	ip	5 min	287	R	Narumi et al., 1983
Apomorphine	3 mg	ip	5 min	280	R	Narumi et al., 1983
Pimozide	1 mg	ip	240 min	100	R	Narumi et al., 1983
α-Methylparatyrosine	250 mg	ip	240 min	100	R	Narumi et al., 1983
Dopamine	15 ng	istr	1 min	180	R	Lautie et al., 1981
Apomorphine	2.5 mg	ip	10 min	177	R	Puri et al., 1978
Apomorphine	3.0 mg	ip	5 min	150	M	Wood et al., 1988b
Apomorphine	1 mg	sc	10 min	145	R	Biggio et al., 1977c
	1 μg	istr	6 min	155	R	Biggio and Guidotti, 1977
Apomorphine	3 mg	ip	15 min	169	R	Mailman et al., 1979
Apomorphine	3 mg	ip	30 min	209	R	Burkard et al., 1976
	10 mg	ip	15 min	319	R	Burkard et al., 1976
Apomorphine	10 mg	ip	15 min	285	R	Mohler et al., 1981
Apomorphine	5 mg	ip	30 min	415	R	Breese et al., 1979a
Apomorphine	0.29 mg	ip	30 min	100	R	Iyengar et al., 1989
Apomorphine	0.86 mg	ip	30 min	172	R	Iyengar et al., 1989
Apomorphine	5.74 mg	ip	30 min	250	R	Iyengar et al., 1989
Apomorphine	14.4 mg	ip	30 min	394	R	Iyengar et al., 1989
CGS 15855	0.2 mg	ip	30 min	100	R	Iyengar et al., 1989
CGS 15855	0.4 mg	ip	30 min	100	R	Iyengar et al., 1989
CGS 15855	1.0 mg	ip	30 min	100	R	Iyengar et al., 1989
CGS 15855	4.0 mg	ip	30 min	283	R	Iyengar et al., 1989
CGS 15855	10.0 mg	ip	30 min	433	R	Iyengar et al., 1989
CGS 15855	30.0 mg	ip	30 min	379	R	Iyengar et al., 1989
Methylphenidate	5 mg	ip	30 min	250	R	Breese et al., 1979a
Amphetamine	2 mg	ip	30 min	266	R	Breese et al., 1979a
Haloperidol	1 mg	ip	30 min	49	R	Breese et al., 1979a
Haloperidol	6 μg	istr	30 min	47	R	Breese et al., 1979a
Haloperidol	6 μg	icer	30 min	100	R	Breese et al., 1979a
Chlorpromazine	1 mg	ip	30 min	50	R	Breese et al., 1979a
(+)Butaclamol	1 mg	ip	30 min	33	R	Breese et al., 1979a
(−)Butaclamol	1 mg	ip	30 min	100	R	Breese et al., 1979a
(+)Sulperide	50 mg	ip	30–120 min	100	R	Corda et al., 1979
(−)Sulperide	50 mg	ip	30–120 min	50	R	Corda et al., 1979
	10 μg	istr	30 min	50	R	Corda et al., 1979
Haloperidol	2 mg	ip	60 min	41	R	Burkard et al., 1976
Haloperidol	5 mg	po	30 min	53	R	Mohler et al., 1981
Bromocriptine	15 mg	ip	30 min	100	R	Breese et al., 1978
Clozapine	15 mg	ip	30 min	100	R	Mailman et al., 1979
Chlorpromazine	6 mg	ip	30 min	48	R	Mailman et al., 1979
Fluoxetine	10 mg	ip	45 min	100	M	Chung, 1983
5-HTP	100 mg	ip	45 min	100	M	Chung, 1983
Cinanserin	5 mg	ip	45 min	100	M	Chung, 1983
Cyproheptadine	1 mg	ip	15 min	100	M	Chung, 1983
Lysergic acid	2 mg	ip	10 min	318	R	Burkard et al., 1976
5-Methyl-dimethyl-tryptamine	10 mg	ip	10–30 min	240	R	Lykouras et al., 1980
Reserpine	10 mg	ip	180 min	25	M	Rubin and Ferrendelli, 1977
Reserpine	10 mg	ip	16 h	50	R	Burkard et al., 1976
Propranolol	10 mg	ip	30 min	100	R	Narumi et al., 1983

TABLE 3—Continued

Drug	Dose (kg)	Route	Time	cGMP (% control)	Rat/ mouse	Reference
Propranolol	6 mg	ip	40 min	100	M	P. L. Wood, unpublished results
Isoproterenol	100 μg	ivt	15 min	100	R	Haidamous et al., 1980
Phenoxybenzamine	5 mg	ip	45 min	21	M	Chung, 1983
Phenoxybenzamine	10 mg	ip	30 min	45	R	Haidamous et al., 1980
Phentolamine	10 mg	ip	30 min	62	R	Haidamous et al., 1980
Yohimbine	7 mg	ip	30 min	100	R	Haidamous et al., 1980
Piperoxan	7 mg	ip	30 min	100	R	Haidamous et al., 1980
Norepinephrine	16 μg	ivt	30 s	142	R	Haidamous et al., 1980
Methoxamine	250 μg	ivt	15 min	128	R	Haidamous et al., 1980
Phenylephrine	200 μg	ivt	15 min	130	R	Haidamous et al., 1980
Clonidine	70 μg	ivt	15 min	68	R	Haidamous et al., 1980
Clonidine	1 mg	ip	20 min	40	R	Haidamous et al., 1980
Diphenhydramine	10 mg	ip	15 min	100	M	Dinnendahl and Gumulka, 1977
Kainate	2 μg	istr	24–72 h	20	R	Biggio et al., 1978a
Kainate	1 μg	istr	0.5 min	71	R	Lautie et al., 1981
Glutamate	600 μg	istr	0.5 min	66	R	Lautie et al., 1981
Cholinergics						
Oxotremorine	5 mg	ip	5 min	354	M	Rubin and Ferrendelli, 1977
Oxotremorine	2 mg	ip	10 min	503	M	Opmeer et al., 1976
Oxotremorine	5 mg	sc	1 min	122	M	Ferrendelli et al., 1970
Oxotremorine	5 mg	sc	3 min	178	M	Ferrendelli et al., 1970
Oxotremorine	5 mg	sc	5 min	169	M	Ferrendelli et al., 1970
Oxotremorine	5 mg	sc	10 min	100	M	Ferrendelli et al., 1970
Oxotremorine	5 mg	ip	5 min	165	M	Wood et al., 1988b
Acetylcholine	16 μg	istr	1 min	66	R	Lautie et al., 1981
Oxotremorine	5 mg	ip	10 min	187	M	Wood et al., 1982
Pilocarpine	8 mg	ip	10 min	177	R	Puri et al., 1978
Arecoline	7.5 mg	sc	30 min	317	M	Gumulka et al., 1979
Arecoline	5 mg	ip	5 min	100	R	Dodson and Johnson, 1979
Arecoline	10 mg	ip	5 min	100	R	Dodson and Johnson, 1979
Arecoline	20 mg	ip	5 min	290	R	Dodson and Johnson, 1979
Arecoline	30 mg	ip	5 min	240	R	Dodson and Johnson, 1979
Trihexyphenidyl	18 mg	ip	20 min	100	R	Biggio et al., 1977c, d
Atropine	50 mg	ip	25 min	100	R	Mailman et al., 1979
Atropine	5 mg	ip	30 min	100	R	Dodson and Johnson, 1979
Atropine	60 mg	sc	60 min	85	M	Ferrendelli et al., 1970
Atropine	120 mg	sc	60 min	51	M	Ferrendelli et al., 1970
Atropine	240 mg	sc	60 min	39	M	Ferrendelli et al., 1970
Benztropine	5 mg	ip	15 min	100	R	Costa et al., 1974
Nicotine	0.25 mg	ip	5 min	300	R	Dodson and Johnson, 1979
Nicotine	0.5 mg	ip	5 min	300	R	Dodson and Johnson, 1979
Nicotine	1 mg	ip	5 min	360	R	Dodson and Johnson, 1979
Nicotine	5 mg	ip	5 min	496	R	Dodson and Johnson, 1979
Opiates						
Morphine	20 mg	ip	30 min	158	M	Askew and Charalampous, 1976
Morphine	10 mg	ip	10 min	159	M (C57)	Racagni et al., 1979
Morphine	10 mg	ip	10 min	32	M (DBA)	Racagni et al., 1979
Morphine	8 mg	ip	30 min	64	R	Biggio et al., 1977b
Morphine	16 mg	ip	30 min	45	R	Biggio et al., 1977b
Morphine	20 μg	istr	30 min	66	R	Biggio et al., 1977b
Viminol R2	6 mg	ip	30 min	49	R	Biggio et al., 1977b
Viminol S2	6 mg	ip	30 min	100	R	Biggio et al., 1977b
Naltrexone	1 mg	ip	30 min	100	R	Biggio et al., 1977b
l-Ethylketazocine	10 mg	sc	30 min	31	M	P. L. Wood, unpublished results
d-Ethylketazocine	10 mg	sc	30 min	100	M	P. L. Wood, unpublished results

TABLE 3—Continued

Drug	Dose (kg)	Route	Time	cGMP (% control)	Rat/ mouse	Reference
Morphine	5 mg	ip	15 min	56	R	Katz and Catravas, 1976
Morphine	45 mg	ip	15 min	31	R	Katz and Catravas, 1976
Morphine	90 mg	ip	15 min	24	R	Katz and Catravas, 1976
D-Ala-Leu enkephalin amide	10 μg	istr	60 min	80	R	Biggio et al., 1978c
D-Ala-Leu enkephalin amide	25 μg	istr	60 min	51	R	Biggio et al., 1978c
D-Ala-Leu enkephalin amide	50 μg	istr	60 min	39	R	Biggio et al., 1978c
TRH peptides						
TRH	10 mg	ip	10 min	175	R	Mailman et al., 1979
DN-1417	3 mg	ip	5 min	550	R	Narumi et al., 1983
DN-1417	10 mg	ip	5 min	700	R	Narumi et al., 1983
DN-1417	10 mg	ip	5 min	140	M	Wood et al., 1988b
TRH	3 mg	ip	5 min	260	R	Narumi et al., 1983
TRH	10 mg	ip	5 min	475	R	Narumi et al., 1983
MeTRH	4 mg	iv	30 min	195	R	Rinehart et al., 1986
DN-1417	10 mg	iv	30 min	295	R	Rinehart et al., 1986
MK-771	10 mg	iv	30 min	305	R	Rinehart et al., 1986
RX 77368	3 mg	iv	30 min	360	R	Rinehart et al., 1986
CCK peptides						
CCK-8 sulfate	1 mg	sc	10 min	50	M	Wood et al., 1988b
CCK-8 sulfate	1 mg	sc	20 min	70	M	Wood et al., 1988b
CCK-8 sulfate	1 mg	sc	40 min	100	M	Wood et al., 1988b
CCK-8 sulfate	0.1 mg	sc	10 min	100	M	Wood et al., 1988b
CCK-8 sulfate	0.6 mg	sc	10 min	64	M	Wood et al., 1988b
CCK-8 sulfate	0.8 mg	sc	10 min	52	M	Wood et al., 1988b
Caerulein	1.0 mg	sc	20 min	58	M	P. L. Wood, unpublished results
Drugs acting at the level of the cerebellum						
GABAergic agents						
Muscimol	10 mg	ip	30 min	65	R	Biggio et al., 1977d
Muscimol	1 μg	icer	30 min	50	R	Biggio et al., 1977d
Muscimol	5 mg	ip	30 min	30	R	Mohler et al., 1981
Aminooxyacetic acid	50 mg	ip	5 h	53	M	Dinnendahl and Gumulka, 1977
Diazepam	5 mg	ip	30 min	60	R	Biggio et al., 1977d
Diazepam	4 μg	icer	30 min	45	R	Biggio et al., 1977d
Diazepam	10 mg	ip	15 min	14	M	Rubin and Ferrendelli, 1977
Diazepam	6 mg	ip	30 min	50	M	P. L. Wood, unpublished results
Diazepam	0.5 mg	ip	15 min	62	R	Costa et al., 1974
Diazepam	1.2 mg	ip	15 min	38	R	Costa et al., 1974
Diazepam	5.0 mg	ip	15 min	26	R	Costa et al., 1974
Diazepam	5 mg	po	30 min	20	R	Mohler et al., 1981
Diazepam	6 mg	ip	30 min	52	R	Wood et al., 1986
CGS 9896	6 mg	ip	30 min	100	R	Wood et al., 1986
CGS 9895	6 mg	ip	30 min	53	R	Wood et al., 1986
Meprobamate	5 mg	po	30 min	63	R	Mohler et al., 1981
Quazepam	5 mg	po	60 min	65	R	Ongini et al., 1982
Flurazepam	5 mg	po	60 min	70	R	Ongini et al., 1982
Chlordiazepam	8 mg	ip	30 min	27	R	Mailman et al., 1979
Zopiclone	2 mg	po	30 min	48	R	Mohler et al., 1981
CL 218,872	1 mg	po	30 min	50	R	Mohler et al., 1981
Clonazepam	2 mg	ip	45 min	33	M	Chung, 1983
Clonazepam	0.2 mg	ip	60 min	61	M	Lust et al., 1978
Alprazolam	5 mg	ip	30 min	39	M	P. L. Wood, unpublished results
Midazolam	10 mg	ip	30 min	49	R	Mohler et al., 1981
Chlordiazepoxide	10 mg	ip	30 min	44	R	Mohler et al., 1981
Valproate	400 mg	ip	60 min	16	M	Lust et al., 1978
Baclofen	10 mg	ip	60 min	21	M	Gumulka et al., 1979
Picrotoxin	2 mg	sc		215	M	Gumulka et al., 1979
Picrotoxinin	0.47 mg	iv	30 min	170	R	Morgan and Pfeil, 1984

TABLE 3—Continued

Drug	Dose (kg)	Route	Time	cGMP (% control)	Rat/ mouse	Reference
Isoniazid	200 mg	sc	30 min	267	M	Gumulka et al., 1979
Isoniazid	300 mg	ip	45 min	275	R	Biggio et al., 1977c, d
Picrotoxin	2 mg	sc	20 min	426	M	Opmeer et al., 1976
Picrotoxin	4 mg	sc	30 min	175	R	Costa et al., 1974
Picrotoxin	2.5 mg	iv	7 min	240	M	Wood et al., 1988b
Strychnine	0.84 mg	sc	25 min	100	R	Costa et al., 1974
Ro 5-3663	20 mg	ip	30 min	173	R	Mohler et al., 1981
Flumazenil	0.5–20 mg	po	30 min	100	R	Mohler et al., 1981
Etazolate	5 mg	po	30 min	40	R	Mohler et al., 1981
Flumazenil	2–30 mg	po	30 min	100	M	Burkard et al., 1985
Flumazenil	100 mg	po	30 min	125	M	Burkard et al., 1985
β-CCM	10 mg	iv	5 min	200	M	Burkard et al., 1985
Diazepam	2 mg	po	30 min	50	M	Burkard et al., 1985
β-CCE	2.4 mg	sc	45 min	224	R	Koe and Lebel, 1983
β-CCE	7.7 mg	sc	45 min	276	R	Koe and Lebel, 1983
β-CCE	24 mg	sc	45 min	226	R	Koe and Lebel, 1983
DMCM	0.5 mg	ip	15 min	155	R	Serra et al., 1983
DMCM	1.0 mg	ip	15 min	200	R	Serra et al., 1983
DMCM	3.0 mg	ip	15 min	250	R	Serra et al., 1983
Convulsants/anticonvulsants						
PTZ	60 mg	sc		430	M	Gumulka et al., 1979
PTZ	100 mg	ip	3 min	300	M	Ferrendelli and Kinscherf, 1977
PTZ	40 mg	ip		400	M	Rubin and Ferrendelli, 1977
PTZ	50 mg	ip	5 min	511	M	Opmeer et al., 1976
PTZ	40 mg	ip	5 min	317	R	Costa et al., 1974; 1975
PTZ	50 mg	ip	5 min	240	M	Wood et al., 1988b
Phenobarbital	20 mg	ip	25 min	29	R	Mailman et al., 1979
Phenobarbital	25 mg	ip	30 min	38	R	Costa et al., 1974
Phenobarbital	50 mg	ip	30 min	42	R	Costa et al., 1974
Phenobarbital	13 mg	iv	16 min	39	R	Morgan and Pfeil, 1984
Phenobarbital	51 mg	iv	16 min	18	R	Morgan and Pfeil, 1984
Phenobarbital	40 mg	ip	120 min	40	M	Ferrendelli and Kinscherf, 1977
Ethosuximade	500 mg	ip	45 min	25	M	Ferrendelli and Kinscherf, 1977
Ethosuximade	200 mg	ip	60 min	35	M	Lust et al., 1978
DPH	25 mg	ip	30 min	48	M	Lust et al., 1978
DPH	25 mg	ip	120 min	40	M	Ferrendelli and Kinscherf, 1977
DPH	45 mg	ip	30 min	100	R	Costa et al., 1974
Carbamazepine	25 mg	ip	60 min	21	M	Lust et al., 1978
Depressants						
Ethanol	1.5 g	ip	30 min	23	R	Mailman et al., 1979
Ethanol	1 g	ip	90 min	75	R	Ferko et al., 1982
Ethanol	2 g	ip	90 min	40	R	Ferko et al., 1982
Ethanol	3 g	ip	90 min	11	R	Ferko et al., 1982
Ethanol	3 g	po	30 min	43	R	Mohler et al., 1981
Methaqualone	10 mg	po	30 min	17	R	Mohler et al., 1981
Barbital	25 mg	iv	16 min	67	R	Morgan and Pfeil, 1984
Barbital	100 mg	iv	16 min	21	R	Morgan and Pfeil, 1984
Pentobarbital	5 mg	iv	16 min	38	R	Morgan and Pfeil, 1984
Pentobarbital	15 mg	iv	16 min	14	R	Morgan and Pfeil, 1984
Pentobarbital	50 mg	ip	30 min	33	M	Opmeer et al., 1976
Pentobarbital	12.5 mg	ip	15 min	40	R	Katz and Catravas, 1976
Pentobarbital	25 mg	ip	15 min	29	R	Katz and Catravas, 1976
Pentobarbital	50 mg	ip	15 min	22	R	Katz and Catravas, 1976
Pentobarbital	80 mg	ip	60 min	7	R	Kant et al., 1980

TABLE 3—Continued

Drug	Dose (kg)	Route	Time	cGMP (% control)	Rat/ mouse	Reference
Halothane	1%			10	R	Kant et al., 1980
Halothane	1–4%		15 min	10	M	Nahrwold et al., 1977
Ether			10 min	2	R	Lust et al., 1976
$MgSO_4$	300 mg	ip	10 min	35	R	Lust et al., 1976
Lidocaine	100 mg	sc	30 min	63	M	Tsai et al., 1987
EAA agonists and antagonists						
Kainate	125 ng	ict	12 min	341	M	Wood et al., 1982
Kainate	250 ng	ict	12 min	1263	M	Wood et al., 1982
Quisqualate	10 ng	ict	12 min	835	M	Wood et al., 1982
Domoate	25 ng	ict	12 min	418	M	Wood et al., 1982
N-methyl-D-aspartate	200 ng	ict	12 min	209	M	Wood et al., 1982
Homocysteic acid	25 ng	ict	12 min	319	M	Wood et al., 1982
Glutamate	515 μg	ivt	5 min	292	R	Costa et al., 1974
Glutamate	590 μg	ivt	10 min	195	R	Briley et al., 1979
Kainate	0.3 μg	ivt	10 min	197	R	Briley et al., 1979
AP5	1 μg	ict	12 min	65	M	Wood et al., 1982
AP5	10 μg	ict	12 min	30	M	Wood et al., 1982
cis-PDA	1 μg	ict	12 min	100	M	Wood et al., 1982
cis-PDA	10 μg	ict	12 min	54	M	Wood et al., 1982
D-AP5	32 mg	iv	12 min	30	M	P. L. Wood, unpublished results
L-AP5	32 mg	iv	12 min	61	M	P. L. Wood, unpublished results
AP7	50 mg	iv	12 min	83	M	P. L. Wood, unpublished results
AP7	150 mg	iv	12 min	26	M	P. L. Wood, unpublished results
CGS 19755	10 mg	ip	20 min	30	M	Lehmann et al., 1988b
CGS 19755	10 mg	ip	30 min	30	M	Lehmann et al., 1988b
CGS 19755	10 mg	ip	60 min	30	M	Lehmann et al., 1988b
CGS 19755	10 mg	ip	120 min	100	M	Lehmann et al., 1988b
Tiletamine	5 mg	sc	30 min	24	M	Lehmann et al., 1988b
PK 26124	50 mg	sc	30 min	45	M	Lehmann et al., 1988b
Glycine	50 μg	icb	10 min	239	M	Rao et al., 1990d
Glycine	200 μg	icb	10 min	427	M	Rao et al., 1990d
Glycinamide	100 μg	icb	10 min	174	M	Rao et al., 1990d
Glycinamide	400 μg	icb	10 min	676	M	Rao et al., 1990d
Adenosine agonists and antagonists						
CHA	3 mg	po	60 min	70	M	Wood et al., 1989b
CHA	3 mg	po	120 min	35	M	Wood et al., 1989b
CHA	10 mg	po	60 min	70	M	Wood et al., 1989b
CHA	10 mg	po	120 min	37	M	Wood et al., 1989b
R-PIA	3 mg	po	60 min	100	M	Wood et al., 1989b
R-PIA	3 mg	po	120 min	100	M	Wood et al., 1989b
R-PIA	10 mg	po	60 min	40	M	Wood et al., 1989b
R-PIA	10 mg	po	120 min	60	M	Wood et al., 1989b
NECA	3 mg	po	60 min	100	M	Wood et al., 1989b
NECA	3 mg	po	120 min	100	M	Wood et al., 1989b
NECA	10 mg	po	60 min	62	M	Wood et al., 1989b
NECA	10 mg	po	120 min	70	M	Wood et al., 1989b
CPDX	25 mg	ip	135 min	100	M	Wood et al., 1989b

* Abbreviations: AP5, aminophosphonopentanoate; AP7, aminophosphonohetanoate; CCE, ethyl β-carboline-3-carboxylate; CCM, methyl β-carboline-3-carboxylate; DMCM, methyl 6,7-dimethyoxy-4-ethyl-β-carboline-3-carboxylate; DN 1417, γ-butyrolactone-γ-carbonyl-L-histidyl-L-proline amide; DPH, diphenylhydantoin; icb, intracerebellar; ict, intracisternal; ivt, intraventricular; MK 771, L-pyro-2-aminodipyl-L-histidyl-L-thiazolidine-4-carboxamide; PTZ, pentylenetetrazol; RX 77368, L-pyroglutamyl-L-histidyl-3,3-dimethyl proline amide; ip, intraperitoneal; R, rat; M, mouse; istr, intrastriatal; sc, subcutaneous; icer, intracerebellar; po, by mouth; iv, intravenous; CHA, cyclohexyladenosine; CPDX, 8-cyclopentyl-1,3-dipropylxanthine; NECA, N-ethylcarboxymidoadenosine; PIA, phenylisopropyladenosine.

cultures supported these autoradiographic studies. Furthermore, in vivo pharmacological studies with the adenosine agonists, cyclohexyladenosine, N-ethylcarboxamidoadenosine, and R-phenylisopropyladenosine, and the selective A_1 antagonist, 8-cyclopentyl-1,3-dipropylxanthine, demonstrated that adenosine-dependent decreases in cerebellar cGMP were A_1 receptor mediated (Wood et al., 1989b).

Although these decreases in cerebellar cGMP were probably mainly evoked via A_1 receptors present on granule cells, the parallel inhibitory effects of these drugs on nigrostriatal dopamine release (Wood et al., 1989b) also may have contributed to some of the net effect, via decreased mossy fiber input to the cerebellum (section V.B.1).

4. Ethanol. Ethanol has been shown to decrease baseline levels of cerebellar cGMP (Dodson and Johnson, 1979; Ferko et al., 1982; Mailman et al., 1979; Mohler et al., 1981; Volicer and Hurter, 1977; Volicer and Klosowicz, 1979) with no tolerance being observed after 1 week of chronic treatment (Dodson and Johnson, 1980), although tolerance has been reported after 12 days of treatment (Breese et al., 1979b). However, during alcohol withdrawal, significant increases in cerebellar cGMP (Ferko et al., 1982) and an increased sensitivity to the depressant actions of alcohol on cGMP (Breese et al., 1979b) were noted.

A role for the motor-depressant actions of alcohol in the ethanol-dependent decreases in cGMP has been suggested (Breese et al., 1979b); however, in rats paralyzed with *d*-tubocurarine and mechanically ventilated, alcohol still significantly depressed cGMP levels in the cerebellum.

In addition to decreasing basal cerebellar cGMP, ethanol also antagonizes harmaline-dependent increases in cGMP (Rappaport et al., 1984), suggesting an antagonism of EAA-mediated transmission in the cerebellum (section III.B.6). Furthermore, the mechanism of action of ethanol, as assessed in granule cell cultures, appears to involve antagonism of NMDA-mediated activation of guanylate cyclase (Hoffman et al., 1989a,b). In support of this mechanism of action, the benzodiazepine receptor antagonist, flumazenil, did not alter the depressant effects of ethanol on cerebellar cGMP, indicating a lack of GABAergic involvement in the actions of ethanol (Mohler et al., 1981).

Chronic lithium treatment (2 mEq of LiCl/kg for 10 days) has been shown to block the decreases in cGMP induced by 3 g/kg of ethanol (Hunt and Goldman, 1979); however, under these conditions the blood levels of ethanol were reduced to 35% of those in rats not receiving lithium.

5. Barbiturates and anesthetics. Pentobarbital (Dodson and Johnson, 1980; Kant et al., 1980; Katz and Catravas, 1976; Mailman et al., 1979; Morgan and Pfeil, 1984; Opmeer et al., 1976), phenobarbital (Ferrendelli and Kinscherf, 1977; Mailman et al., 1979; Morgan and Pfeil, 1984), and barbital (Lane and Morgan, 1984) dose and time dependently (Morgan and Pfeil, 1984) decrease basal cerebellar cGMP and tolerance develops to these actions. Interestingly, there is a dissociation between the time course of recovery to the motor-depressant and cGMP effects of pentobarbital, indicating a lack of correlation between motor activity and cerebellar cGMP levels (section II.E.1; Morgan and Pfeil, 1984). The effects of phenobarbital were not reversed by the benzodiazepine receptor antagonist, flumazenil (Mohler et al., 1981), indicating a lack of involvement of benzodiazepine receptors in the actions of this drug. Also of interest, barbital withdrawal from dependent rats (8 weeks) has been shown to result in a selective supersensitivity to kainate-dependent increases in cerebellar cGMP (McCaslin and Morgan 1989); there was no augmentation of the NMDA or quisqualate response (III.B.6). These data suggest a possible role for barbiturate modulation of EAA pathways in vivo.

The general anesthetics, halothane (Kant et al., 1980; Nahrwold et al., 1977) and ether (Lust et al., 1976), also dose dependently decreased basal cGMP levels. Similarly, the local anesthetic, lidocaine, decreased cGMP after parenteral administration (table 2).

6. Excitatory amino acid receptor modulators. a. EXCITATORY AMINO ACID AGONISTS. Within the CNS there are three major EAA receptor subtypes as characterized by their selective agonists: kainate, quiqualate, and NMDA. Additionally, the NMDA receptor is a macromolecular complex that also contains a positive allosteric glycine site and a negative allosteric PCP site (Bertlino et al., 1988; Wood et al., 1989c). Within the cerebellum (Cotman et al., 1987; Olson et al., 1987), autoradiographic studies have demonstrated dense populations of quisqualate receptors on Purkinje cell dendrites and kainate receptors on granule cells. Electrophysiological studies (DuPont et al., 1984) have demonstrated that these dendritic quisqualate receptors are functionally coupled to neuronal activity changes. In brain slices from Nervous mice, possessing reduced Purkinje cell populations (table 1), kainate still stimulates cGMP formation (Schmidt and Nadi, 1977); this finding is consistent with the presence of kainate receptors on granule cells. Small numbers of NMDA receptors also were shown to be resident on granule cells, consistent with data from granule cell cultures (section II.F.3). Biochemical and electrophysiological studies also support the presence of NMDA receptors on the terminals of afferent noradrenergic nerve endings in the cerebellum (Marwaha et al., 1980, 1981; Rao et al., 1990h; Wood and Rao, 1990; Yi et al., 1988).

Presumably, as a result of these strategic receptor localizations, NMDA, quisqualate, and kainate, after intraventricular (McCaslin and Morgan, 1989), intracisternal (Wood et al., 1982), and direct intracerebellar

(Wood et al., 1987, 1989a,d; Wood and Rao 1989; Wrobleweski et al., 1987) injections, increase cerebellar cGMP in a dose-dependent manner (fig. 2). Analyses of the interactions of NMDA with its receptor also suggest that two to three molecules of NMDA are required for activation of each NMDA receptor unit (Wood et al., 1989a), an observation previously reported for the interaction of GABA with the GABA/benzodiazepine receptor complex (Brookes and Werman, 1973).

Interestingly, during barbital withdrawal from dependent rats, there is a selective sensitization of cerebellar cGMP responses to kainate but not to NMDA or quisqualate (McCaslin and Morgan, 1989), suggesting an independent kainate receptor action. The increases in cerebellar cGMP induced by intracerebellar kainate peak at 30 min and are maintained for 5 h (Biggio et al., 1978d). However, by 24 h, when cell death has occurred, cGMP levels decrease to 20% of control and are maintained at this low level for at least 72 h (Biggio et al., 1978d). Additionally, these kainate lesions block harmaline- and isoniazid-dependent increases in cerebellar cGMP (Biggio et al., 1978d).

b. N-METHYL-D-ASPARTATE-ASSOCIATED GLYCINE AGONISTS. The NMDA-associated glycine receptor is a positive allosteric site on the NMDA receptor complex (Johnson and Archer, 1987; Monaghan et al., 1988) and is analogous with the benzodiazepine/GABA receptor complex (Wood et al., 1989c). Glycine itself, after intraventricular (Danysz et al., 1989;) or direct intracerebellar (Rao et al., 1990d) injection, increases cerebellar cGMP levels. Similarly, D-serine, a stereospecific agonist for the glycine receptor, which is not a substrate for amino acid uptake carriers (Balcar and Johnson, 1973), dose dependently increases cerebellar cGMP with an efficacy approximately one-half that of NMDA (Wood et al., 1989a). The partial glycine agonist, D-cycloserine (Emmett et al., 1990), also increases cGMP levels after either parenteral or direct intracerebellar drug administration, but in these cases the drug produces bell-shaped dose-response curves (Monahan et al., 1989; Emmett et al., 1990).

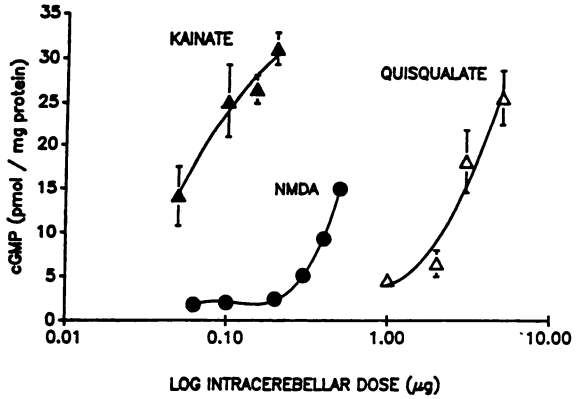

FIG. 2. Log-dose response curves for kainate-, NMDA-, quisqualate-dependent increases in mouse cerebellar cGMP, 10 min after direct intracerebellar injection (Wood et al., 1989a).

The source of endogenous glycine in vivo requires further definition; however, studies of cerebellar astroglia have demonstrated extremely high levels of glycine (Cabier and Pessac, 1987). The anatomical proximity of glial cells to nerve terminals (Hatten et al., 1984; Palay and Chan-Palay, 1974; Reese et al., 1985) suggests that this may be an important pool of glycine for the modulation of NMDA-mediated neurotransmission.

c. ENDOGENOUS EXCITATORY AMINO ACID RELEASE. Although the identity of EAA transmitters in the cerebellum has not been unequivocally demonstrated, pharmacological tools are available to activate EAA-utilizing pathways. These include harmaline which activates climbing fiber inputs to the cerebellum (Guidotti et al., 1975; Wood et al., 1982) and pentylenetetrazol which inhibits GABAergic synapses allowing excessive EAA transmission (Wood et al., 1990a). These drugs elicit dose-dependent increases in cerebellar cGMP levels that are antagonized by competitive NMDA antagonists (Wood et al., 1982, 1987, 1989c), noncompetitive NMDA antagonists (Wood et al., 1987, 1989c), NMDA-associated glycine receptor antagonists (Wood et al., 1989d), and inhibitors of NO synthase (Wood et al., 1990b; Wood, 1990; Wood and Rao, 1990).

d. ROLE OF NITRIC OXIDE. The biosynthesis of NO from arginine, via NO synthase (Bredt and Snyder, 1990), is a signal transduction mechanism (section III.A) that has been shown to be stimulated by EAA agonists in vitro (Bredt and Snyder, 1989; Garthwaite et al., 1988, 1989a,b). Similarly, the NO synthase inhibitor, N-monomethyl-L-arginine, has been shown to decrease basal cGMP levels and to block NMDA-, quisqualate-, and kainate-dependent increases in cGMP in vivo (Wood et al., 1990b; Wood and Rao, 1990; Wood, 1990; table 4). These data indicate that NO formation is stimulated by all three EAA receptor subtypes in vivo and that the diffusible intercellular messenger, NO, then activates guanylate cyclase in a number of cerebellar cell types (section III.A). The Ca^{2+} dependency of NO synthase (Bredt and Snyder, 1990) is consistent with prior reports that pharmacological activation of cerebellar cGMP, via a variety of mechanisms, was Ca^{2+} dependent.

These studies encompassed cerebellar slices (Ferrendelli et al., 1973), cultured granule cells (Novelli and Henneberry, 1987), and in vivo studies with intracerebellar injections of the Ca^{2+} antagonist, diltiazem (P. L. Wood, unpublished results).

e. ROLE OF NORADRENERGIC AFFERENTS. The cerebellum receives an extensive noradrenergic fiber input from the locus coeruleus and other pontine noradrenergic nuclei (Bloom et al., 1971; Olsen and Fuxe, 1971). Additionally, biochemical studies with cerebellar slices have shown that presynaptic NMDA/PCP receptors regulate norepinephrine release from these nerve endings in the cerebellum (Yi et al., 1988). In vivo, norepinephrine and selective α_1-noradrenergic agonists have been shown to

TABLE 4
Modulation of cerebellar cGMP by the NO synthetase inhibitor, NMMA

Drug Treatment (μg, intracerebellar) [mg/kg, sc]	cGMP (% control)
NMMA (10)	68
NMMA (25)	65
NMMA (50)	53
NMMA (100)	54
NMMA (100) + L-arginine (200)	100
L-Arginine (200)	100
Quisqualate (5)	1184
Quisqualate (5) + NMMA (100)	228
Kainate (0.3)	1199
Kainate (0.3) + NMMA (100)	482
D-Serine (200)	279
D-Serine (200) + NMMA (25)	100
D-Serine (200) + NMMA (100)	100
Harmaline [100]	935
Harmaline [100] + NMMA (50)	277
PTZ [50]	395
PTZ [50] + NMMA (50)	100

* Abbreviations: NMMA, N-monomethyl-L-arginine; PTZ, pentylenetetrazol (Wood et al., 1990b). Intracerebellar antagonists treatments were coinjections with agonist treatments which were all 10 min prior to microwave fixation.

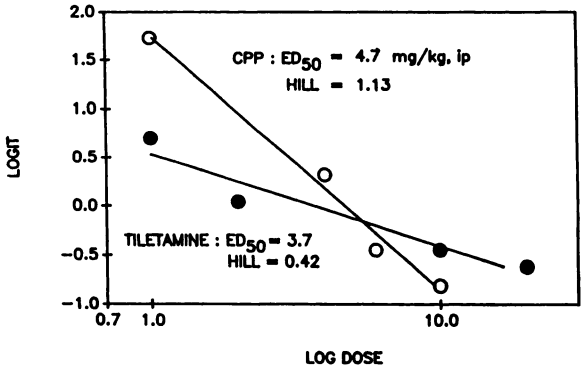

FIG. 3. Logit-log dose-response curves for decrements in basal cerebellar cGMP induced by the competitive NMDA antagonist, (CPP), and the noncompetitive NMDA receptor antagonist, tiletamine (30 min).

increase cerebellar cGMP (Haidamous et al., 1980), whereas α_1 antagonists decrease cGMP levels (Chung, 1983; Haidamous et al., 1980). These data suggest that there might be a tonic noradrenergic input which positively modulates cGMP levels via an α_1 receptor subtype and that the terminals of these noradrenergic afferent fibers can be positively driven by NMDA receptor agonists. Such a hypothesis is supported by the observations that the nonselective α_1 antagonist, clozapine, and the selective antagonist, WB-4101, both can antagonize the ability of NMDA, D-serine, harmaline, and pentylenetetrazol to increase cGMP levels (Rao et al., 1990h; Wood and Rao, 1990). Of significance, these α_1 antagonists were unable to modify quisqualate-dependent increases in cGMP (Rao et al., 1990h), which would be consistent with the presence of quisqualate receptors on Purkinje cell dendrites and not on noradrenergic nerve endings (Olson et al., 1987). These data are also consistent with earlier electrophysiological studies from which it was concluded that suppression of cerebellar Purkinje cell firing induced by PCP agonists was due to presynaptic inhibition of norepinephrine release in the cerebellum (Marwaha et al., 1980, 1981; Wang and Lee, 1989).

f. COMPETITIVE AND NONCOMPETITIVE N-METHYL-D-ASPARTATE ANTAGONISTS. A number of linear and rigid phosphonic acid analogues which are competitive NMDA antagonists (Czuczwar and Meldrum, 1982; Lehmann et al., 1988b, 1987) have been examined and all were found to dose dependently decrease basal cGMP levels (fig. 3), thereby demonstrating their ability to antagonize the endogenously released EAA neurotransmitter(s) in the cerebellum (Wood et al., 1982, 1987, 1989c, 1990a; Wood and Rao 1990). These agents also antagonize NMDA-, D-serine-, harmaline-, and pentylenetetrazol-dependent increases in cerebellar cGMP (tables 5 and 6). Noncompetitive NMDA antagonists, which act at the negatively coupled PCP receptor component of the NMDA receptor complex (Wong et al., 1986), also decrease basal cerebellar cGMP levels (fig. 3) in a dose-dependent manner (Wood et al., 1987, 1989a,c; Wood and Rao, 1990). These agents also antagonize the actions of D-serine, NMDA, harmaline, and pentylenetetrazol but not those of kainate or quisqualate.

g. N-METHYL-D-ASPARTATE-ASSOCIATED GLYCINE RECEPTOR ANTAGONISTS. The NMDA-associated glycine receptor antagonist, HA-966 (Bonta et al., 1971; Menon, 1981; Wood et al., 1989d), unlike competitive and noncompetitive NMDA antagonists, does not alter basal cerebellar cGMP levels (Wood et al., 1989c). However, this agent is able to antagonize the increases in cGMP elicited by NMDA, D-serine, harmaline, and pentylenetetrazol (table 6). Similar to competitive and noncompetitive NMDA antagonists, this agent is unable to antagonize the effects of kainate or quisqualate.

h. NONSELECTIVE EXCITATORY AMINO ACID ANTAGONISTS. The nonselective EAA antagonists, 6,7-dinitroquinoxaline-2,3-dione and 6-nitro,7-cyanoquinoxaline-2,3-dione, antagonize the actions of quisqualate on cerebellar cGMP (Rao et al., 1990e; Wood et al., 1989d). However, these agents also block D-serine and NMDA actions, presumably via their potent antagonist actions at the NMDA-associated glycine receptor (Kessler et al., 1989; Rao et al., 1990e; table 6).

i. POLYAMINES. The endogenous polyamines spermine and spermidine (table 6), after direct intracerebellar administration, do not alter basal cerebellar cGMP levels but do antagonize the effects of NMDA and quisqualate receptor activation (Rao et al., 1990b,c; Wood and Rao, 1990) as well as endogenous EAA release evoked by harmaline (Rao et al., 1990c). This nonselective profile was suggested to possibly involve polyamine-dependent decreases in intracellular calcium (Rao et al., 1990c).

j. SIGMA LIGANDS. A number of novel sigma receptor

TABLE 5

Antagonism by drugs of lesions on pharmacologically induced increases in cerebellar cGMP

Antagonist†	Agonist*							
	Apo	Amph	TRH	Oxo	Harm	Picro	Ison	PTZ
3-AP	No	–	No	–	Yes	–	No	–
Kainate	Yes	–	–	–	No	–	No	–
AMPT	No	Yes	Yes	–	–	–	–	–
Haloperidol	Yes	–	No	–	No	–	–	–
Pimozide	Yes	Yes	No	–	–	–	–	–
Propranolol	–	No	No	–	–	–	–	–
Atropine	Yes	–	No	Yes	No	Partial	No	No
Baclofen	–	–	–	–	–	Yes	Yes	No
Diazepam	Yes	–	–	Yes	Yes	Yes	Yes	Yes
Pentobarb	–	–	–	Yes	Yes	Yes	–	Yes
CCK	Yes	Yes	Yes	Yes	Yes	No	–	No
CPP	–	Yes	–	Yes	Yes	Yes	–	Yes
Kainate	–	–	–	–	Yes	–	Yes	–

* Agonist treatments included: apomorphine (Apo) a dopamine agonist; amphetamine (Amph) a dopamine releaser; thyropropin-releasing hormone (TRH); oxotremorine (Oxo) or arecoline as a muscarinic agonist; harmaline (Harm) as an activator of climbing fibers; picrotoxin (Picro) as a GABA-A antagonist; isoniazid (Ison) as an inhibitor of GABA synthesis; and pentylenetetrazol (PTZ) as a convulsant; –, not tested.

† Antagonist: 3-acetylpyridine lesions of inferior olive to interrupt climbing fibers (Biggio et al., 1977c, d; Guidotti et al., 1975; Mailman et al., 1979); kainate lesions of striatum to interrupt mossy fiber pathways (Biggio et al., 1978a); α-methylparatyrosine (AMPT) treatments to inhibit dopamine synthesis (Narumi et al., 1983); haloperidol to block D-2 dopamine receptors (Biggio et al., 1977d, 1978c; Mailman et al., 1979); pimozide to block D-2 receptors (Narumi et al., 1983); whereas no reversal of TRH was observed, the actions of the TRH analogue DN-1417 were reversed; propranolol to block β-adrenergic receptors (Narumi et al., 1983); atropine or trihhexyphenidyl to block muscarinic receptors (Biggio et al., 1977c, d; Burkard et al., 1985; Mailman et al., 1979; Opmeer et al., 1976); baclofen as an agonist of GABA-B receptors (Gumulka et al., 1979); diazepam as a benzodiazepine agonist to potentiate GABA-A receptors (Biggio et al., 1977c, d; Mao et al., 1975a; Opmeer et al., 1976); pentobarbital to potentiate GABA-A receptors via a barbiturate-binding site (Opmeer et al., 1976); cholecystokin-8-sulfate (Kageyama and Kurosawa, 1989; Wood et al., 1988b); CPP, AP5, AP7 or CGS 19755 to antagonize excitatory amino acid receptors (Lehmann et al., 1987, 1988a, b; Wood et al., 1987); kainate lesions of cerebellum to destroy granular cells (Biggio et al., 1978d).

TABLE 6

Antagonists of EAA-dependent increases in mouse cerebellar cGMP levels

Antagonist*	Agonist					
	NMDA	Quisqualate	Kainate	Harmaline	PTZ	Oxotremorine
Competitive NMDA	Yes	NT	NT	Yes	Yes	Yes
Noncompetitive NMDA	Yes	No	No	Yes	Yes	Yes
HA-966	Yes	No	No	Yes	Yes	NT
Nonselective EAA	Yes	Yes	NT	Yes	Yes	NT
Polyamines	Yes	Yes	Yes	Yes	Yes	NT
Sigma ligands	Yes	No	NT	Yes	NT	NT
Ifenprodil	Yes	Yes	NT	Yes	NT	NT

* Competitive NMDA antagonists: CPP and CGS 19755 (Lehmann et al., 1987; 1988a, b; Wood et al., 1987); noncompetitive NMDA antagonists: MK-801, PCP, dexoxadrol (Lehmann et al., 1986; Lehmann and Wood, 1988; Wood et al., 1987); HA-966, competitive glycine antagonist (Bonta et al., 1971; Wood et al., 1989a, c, d, 1990a; Wood and Rao, 1990); nonselective EAA antagonists: 6,7-dinitroquinoxaline and 6-nitro,7-cyanoquinoxaline-2,3-dione (Birch et al., 1988; Rao et al., 1990e; Wood and Rao, 1990); Polyamines: spermine and spermidine (Rao et al., 1990b, c; Wood and Rao, 1990); sigma receptor ligands: BMY 14802 and opipramol (Rao et al., 1990a; Wood and Rao 1990); ifenprodil, mixed sigma/polyamine receptor ligands: ifenprodil and SL 76002 (Carter et al., 1988, 1999; Rao et al., 1989; Wood and Rao, 1990). NT, not tested.

ligands have been observed to antagonize increases in cerebellar cGMP elicited by activation of NMDA and NMDA-associated glycine receptors (Rao et al., 1990a,f; Wood and Rao, 1990). BMY 14802, an apparently selective sigma ligand, although slightly elevating basal cGMP levels, also selectively antagonizes NMDA-dependent increases in cGMP without altering cGMP responses to quisqualate. This effect on NMDA receptor action is centrally mediated as evidenced by efficacy after intraventricular injections (Rao et al., 1990a); however, BMY 14802 was inactive after direct intracerebellar injection, suggesting an extracerebellar locus of action (Rao et al., 1990a,g). The mechanism and site of action of sigma receptor modulation of NMDA receptor function, therefore, requires more intense investigation.

IV. Climbing Fiber System

The climbing fiber pathway is a system with a discrete origin in the inferior olive, which ascends into the cerebellum to innervate Purkinje cells and also sends collaterals to the granule cell layer (Palay and Chan-Palay, 1974; fig. 1). As discussed in section III.A, this appears to be an EAA-utilizing pathway.

The climbing fiber system is unique in that it can be selectively activated by the alkaloid, harmaline (Biggio et al., 1977c; Guidotti et al., 1975; Wood et al., 1982,

1989c, 1990a), and is lesioned by the toxin, 3-acetylpyridine (Balaban, 1985; Guidotti et al., 1975). The actions of harmaline involve enhanced firing of the inferior olive (LaMarre et al., 1971) which, in turn, leads to increased cerebellar cGMP levels (Biggio et al., 1977c; Guidotti et al., 1975; Wood et al., 1982, 1989c, 1990a). The actions of harmaline involve increased cGMP in both the vermis and hemispheres of the cerebellum (Guidotti et al., 1975; Rubin and Ferrendelli, 1977), with approximately 80% of the tissue change occurring in the molecular layer and 20% in the granular layer (Rubin and Ferrendelli, 1977). The mechanism of action of harmaline remains undefined at this time, but it is not a result of its monoamine oxidase-inhibiting properties because other monoamine oxidase inhibitors, such as pargyline and deprenyl, do not alter cerebellar cGMP (Costa et al., 1974; Mao et al., 1974a). No benzodiazepine receptor involvement is evident, because the benzodiazepine receptor antagonist, flumazenil, does not alter the effects of harmaline (Mohler et al., 1981) and the actions of harmaline are independent of motor activity changes as examined in *d*-tubocurarine-paralyzed animals (Lundberg et al., 1979).

In a number of pharmacological studies (table 5), the actions of harmaline have been shown to be antagonized by diazepam and pentobarbital (Dodson and Johnson, 1979), presumably via enhanced GABAergic transmission within the cerebellum (section III. B.1); competitive NMDA receptor antagonists such as CPP (Lehmann and Wood, 1988; Lehmann et al., 1987) and CGS 19755 (Lehmann et al., 1988a,b); noncompetitive NMDA antagonists (Wood et al., 1987); antagonists of NMDA-associated glycine receptors (Wood et al., 1989d), presumably via inhibition of NMDA-mediated transmission within the cerebellum (section III.B.6); CCK fragments (Wood et al., 1988b, 1989) and the CCK-like peptide caerulein (Kageyama and Kurosawa, 1989), via extracerebellar actions (section V.B.4); alcohol (Rappaport et al., 1984; section III.B.4); 3-acetylpyridine lesions of the climbing fiber pathway (Biggio et al., 1977a; Guidotti et al., 1975; Mailman et al., 1979; section IV); sigma receptor ligands (Rao et al., 1990a; Wood and Rao, 1990; section III.B.6.j); and polyamines (Rao et al., 1990c; section III.B.g.i).

In contrast, the actions of harmaline are not altered by manipulation of cerebellar mossy fiber systems (section V), including the administration of the anticholinergic, atropine (Biggio et al., 1977c; Opmeer et al., 1976); the antidopaminergic, haloperidol (Biggio et al., 1977c); and by kainate lesions of projection cells in the striatum which innervate pontocerebellar mossy fibers (Biggio et al., 1978a).

The toxin, 3-acetylpyridine, is an extremely useful tool in the study of cerebellar function in that it induces an extensive lesion of the cerebellar climbing fiber system (reviewed by Balaban, 1985). Several aspects of the neurochemistry of 3-acetylpyridine lesions have been investigated and indicate that cerebellar aspartate levels are significantly decreased after the lesion occurs, suggesting that the climbing fiber pathway utilizes an EAA as its neurotransmitter (McBride et al., 1978; Nadi et al., 1977). Such lesions remove the incoming climbing fiber activity which decreases the basal tone of the cerebellar cGMP system(s) by 20 (Mailman et al., 1979) to 40% (Biggio et al., 1977c,d; Guidotti et al., 1975). Additionally, these lesions selectively block the actions of harmaline on cerebellar cGMP levels (Biggio et al., 1977c,d; Guidotti et al., 1975; Mailman et al., 1979) without altering the actions of modulators of climbing fibers or intracerebellar pathways. The pharmacological agents not affected by 3-acetylpyridine lesions are discussed in more detail throughout this review, but briefly summarized they include (table 5) apomorphine (Biggio et al, 1977c), TRH (Mailman et al., 1979), isoniazid (Biggio et al, 1977c), haloperidol (Biggio et al., 1977d), diazepam (Biggio et al., 1977d), muscimol (Biggio et al., 1977c,d), and morphine (Biggio et al., 1977d).

V. Mossy Fiber Systems

A. Anatomy/Neurochemistry

The mossy fiber pathways are afferent innervations that synapse almost exclusively on cerebellar granule cells. These inputs consist of the spinocerebellar, pontocerebellar, and vestibulocerebellar systems (Allen and Tsukahara, 1974); unfortunately, our knowledge base of the neurochemistry of these pathways is nonexistent. However, we do have some data regarding the chemical makeup and pharmacology of a striatal system which, via a multisynaptic pathway (fig. 4), modulates the activity of pontocerebellar neurons (Biggio et al., 1978a).

B. Pharmacology

1. Dopaminergic modulators. A number of early studies demonstrated that the dopamine agonist, apomorphine (Biggio et al., 1977c; Breese et al., 1978; 1979a; Burkard et al., 1976; Gumulka et al., 1976; Mohler et al., 1981; Narumi et al., 1983; Puri et al., 1978), the dopamine releasers amphetamine, methamphetamine and methylphenidate (Breese et al., 1978, 1979a; Gumulka et al., 1976; Narumi et al., 1983; Wood et al., 1988b), and the dopamine precursor, L-DOPA, in combination with a peripheral decarboxylase inhibitor (Gumulka et al., 1976), all increased cerebellar cGMP levels. Studies in which intrastriatal injections of apomorphine (Biggio and Guidotti, 1976) and dopamine (Lautie et al., 1981) were used clearly indicated that these dopaminergic effects involved striatal dopaminergic receptors and synapses. The role of central dopamine receptors in these actions was also supported by antagonism of the actions of apomorphine by a number of brain bioavailable dopamine antagonists but not by the peripheral dopamine receptor antagonist, bromocriptine (Breese et al., 1978,

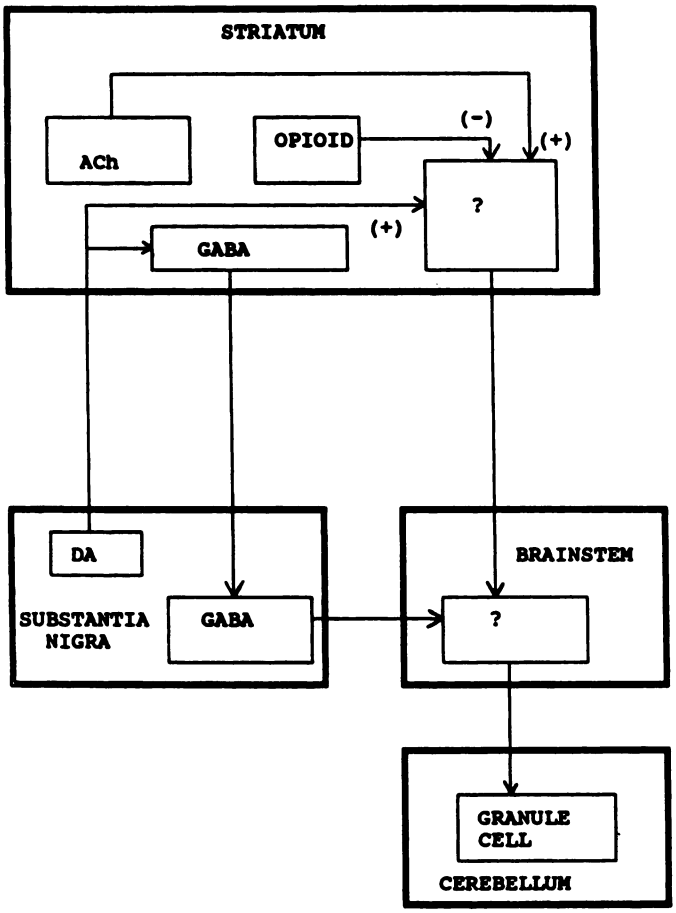

FIG. 4. Proposed polysynaptic circuitry included in the mossy fiber input(s) to the cerebellum, which are modulated by striatal dopaminergic synapses. DA, dopamine; ACh, acetylcholine.

1979a). The importance of the striatum in these drug effects was further validated using kainate lesions of the striatum (Biggio et al., 1978a). In this case, the effects of apomorphine in increasing cerebellar cGMP were blocked by such striatal lesions, whereas the effects of harmaline and isoniazid were unaltered. In addition, it is noteworthy that the kainate lesions of the striatum resulted in time-dependent decreases (6 h = 85% of control, 12 h = 67%, 24 h = 31%, 72 h = 26%) in the basal levels of cerebellar cGMP with no change in cerebellar guanylate cyclase activity (Biggio et al., 1978a).

These data indicate that tonic mossy fiber input to the cerebellum is a major contributor to the basal levels of cGMP measured in this brain area. These data have, therefore, led to the speculation of the existence of a multisynaptic pathway between the striatum and the pontocerebellar mossy fiber system (fig. 4; Biggio et al., 1978a). The kainate lesions support a striatal cell population with efferent fibers reaching the pontine regions; however, the number of synapses in such an output system has not been defined. The enhanced cerebellar cGMP levels measured after activation of this pathway with apomorphine appear to be partially dependent upon motor stimulation, because the increases elicited in rats paralyzed with *d*-tubocurarine and mechanically ventilated were smaller than those occurring in free-moving rats (Breese et al., 1979a; Lundberg et al., 1979). However, there was no direct correlation between locomotor activity and cerebellar cGMP (Breese et al., 1979a).

In contrast to the actions of the dopamine agonists and releasers, dopamine antagonists have been shown to stereospecifically decrease basal cGMP levels (Biggio and Guidotti, 1977; Biggio et al., 1977c; Breese et al., 1978, 1979a; Burkard et al., 1976; Corda et al., 1979). These decreases in cerebellar cGMP are also stereospecifically reproduced by intrastriatal, but not intracerebellar, injections of dopamine antagonists (Biggio et al., 1977d; Biggio and Guidoti, 1977; Breese et al., 1979a; Corda et al., 1979). The actions of both dopamine agonists and antagonists were not altered in animals with lesions produced by 3-acetylpyridine, indicating a lack of involvement of climbing fibers in the observed drug effects (Biggio et al., 1977d). Studies (Biggio et al., 1978c) of chronic neuroleptic treatment (haloperidol, 0.5 mg/g, twice daily for 20 days) have shown tolerance to the decreases in cGMP levels induced by haloperidol treatment. Additionally, these tolerant rats were shown to express enhanced sensitivity to apomorphine-induced cGMP increases, suggesting that cGMP is a sensitive index of the level of striatal dopamine receptor activation (Biggio et al., 1978b). This contention has been supported in studies of the presynaptic to postsynaptic dose-response relationships for the dopamine agonist, apomorphine, and the more selective dopamine autoreceptor agonist, (±)-*trans*-1,3,4,4a,10b-hexahydro-4-propyl-2H[l]benzopyrano[3,4-b]pyridin-9-ol (Iyengar et al., 1989). In these studies, all effective postsynaptic dopamine receptor doses, as assessed by changes in striatal acetylcholine levels, also increased cerebellar cGMP (Iyengar et al., 1989), suggesting modulation of the striato-pontocerebellar mossy fiber pathway.

From these studies, it has been suggested that there is a tonic net excitatory effect on pontocerebellar mossy fibers via striatal output neurons which can be further potentiated by dopamine agonists or releasers. One piece of data inconsistent with this hypothesis is that inhibition of dopamine synthesis with α-methyl-paratyrosine does not alter basal cGMP levels (Narumi et al., 1983). Although these negative data clearly require reevaluation, a similar finding has been reported for 6-hydroxydopamine treatments, which do not alter basal cGMP levels (Mao et al., 1974a). The α-methyl-paratyrosine treatments, however, did antagonize the actions of amphetamine in increasing cerebellar cGMP (Narumi et al., 1983). In both of these studies, the measurement of striatal dopamine content was not reported; therefore, a small functional dopamine pool may have been present and capable of maintaining basal dopaminergic transmission and thus not altering cerebellar cGMP. However, reserpine treatment, which depletes both dopamine and

norepinephrine, does decrease cerebellar cGMP (Rubin and Ferrendelli, 1977).

Another possible explanation for some of the discrepant data, with regard to the tonicity of this dopamine-modulated output from the striatum, is the observation that, in rats habituated to handling, basal cGMP levels are lower than in naive rats and that dopamine antagonists cannot further decrease the cGMP levels in these animals (Corda et al., 1980). These data indicate that the decreases in basal cerebellar cGMP levels measured after dopamine antagonist treatments may well depend upon the degree of stress elevation of basal cGMP levels, a notion consistent with dopaminergic involvement in stress-induced cGMP increases (Dinnendahl and Gumulka, 1977; section II.E.2).

The actions of apomorphine have also been shown to be blocked by pretreatment with the central anticholinergics, trihxyphenidyl (Biggio et al., 1977c) and hyoscine (Burkard et al., 1976), but not by methylatropine, which is not brain bioavailable, indicating a central action of the anticholinergics in blocking apomorphine (Burkard et al., 1976). These data indicate that there is a cholinergic synapse downstream to the dopaminergic synapse in this multisynaptic pathway to the pontocerebellar mossy fiber system. The exact location of the cholinergic synapse involved is currently unknown but is unlikely to be within the striatum (Burkard et al., 1976).

2. Cholinergic modulators. The muscarinic agonists oxotremorine, pilocarpine, and arecoline (Dinnendahl and Stock, 1975; Dodson and Johnson, 1979; Ferrendelli et al., 1970; Gumulka et al., 1976; Opmeer et al., 1976; Puri et al., 1978; Rubin and Ferrendelli, 1977; Wood et al., 1982) as well as the nicotinic agonist, nicotine (Dodson and Johnson, 1979), all dose dependently and time dependently increase cerebellar cGMP levels. Interestingly, the increases in cGMP elicited by oxotremorine were only monitored in the vermis but not the hemispheres of the cerebellum (Rubin and Ferrendelli, 1977). These data suggest that more topographic effects can be observed with cerebellar cGMP changes after mossy fiber activation than is evident with climbing fiber or intracerebellar circuit changes.

In contrast, cholinesterase inhibitors exert more complex effects, in that early (10 min) increases in cerebellar cGMP are followed by decreases at 30–60 min (Dinnendahl and Stock, 1975). These effects may well involve later multisynaptic effects of cholinesterase inhibition but require more in-depth studies.

Antimuscarinics do not alter cerebellar basal cGMP levels (Biggio et al., 1977c,d; Burkard et al., 1976; Costa et al., 1974; Dodson and Johnson, 1979; Mailman et al., 1979; Mao et al., 1974a), except at extremely high doses (Ferrendelli et al., 1970; Rubin and Ferrendelli, 1977). However, at effective antimuscarinic doses, atropine or trihexyphenidyl has been shown to block the increases in cerebellar cGMP elicited by the muscarinic agonist, oxotremorine, (Dinnendahl and Stock, 1975; Ferrendelli et al., 1970; Opmeer et al., 1976) and the dopamine agonist, apomorphine (Biggio et al., 1977c; Burkard et al., 1976). In contrast, the antimuscarinic, methylatropine, which does not cross the blood-brain barrier, does not block the effects of oxotremorine (Opmeer et al., 1976) or apomorphine (Burkard et al., 1976) to increase cerebellar cGMP, clearly indicating that the effects of muscarinic agonists are centrally mediated.

The ganglionic (nicotinic) blockers, mecamylamine and chlorisondamine, do not alter cerebellar cGMP levels in control or cold-stressed rats (Mao et al., 1974a).

3. Thyrotropin-releasing hormone analogues. TRH and the TRH analogues, DN-1417, L-pyroglutamyl-L-histidyl-3,3-dimethyl proline amide, and L-pyro-2-aminodipyl-L-histidyl-L-thiazolidine-4-carboxamide, all increase cerebellar cGMP in rats and mice (Mailman et al., 1979; Narumi et al., 1983; Rinehart et al., 1986). The exact mechanism of action remains undefined for these compounds; however, experiments with central injections of TRH and measurement of TRH levels in the CNS after peripheral administration argue in favor of a CNS locus of action. Studies of lesions produced by 3-acetylpyridine have ruled out a modulatory effect on the climbing fiber system (Mailman et al., 1979).

A number of studies have demonstrated the ability of TRH analogues to release dopamine in the striatum and nucleus acuumbens (Narumi et al., 1983; Wood and Altar, 1988). Such data suggest that TRH analogues might, therefore, modulate cerebellar cGMP via a mossy fiber pathway. Experiments with the tyrosine hydroxylase inhibitor, α-methyl-paratyrosine, support this conclusion in that such treatments block the effects of TRH, DN-1417, and the dopamine releaser, methamphetamine, on cerebellar cGMP (Narumi et al., 1983). Similarly, the D-2 receptor antagonist, pimozide, blocks the effect of DN-1417, apomorphine, and methamphetamine (Narumi et al., 1983). However, D-2 receptor blockade with either pimozide (Narumi et al., 1983) or haloperidol (Mailman et al., 1979) does not block the actions of TRH. These apparently contradictory data require further evaluation, but a modulatory effect of these analogues on mossy fiber systems is suggested at this time. Direct effects of TRH on guanylate cyclase have been discounted (Mailman et al., 1979).

In studies in which artificially ventilated rats paralyzed with *d*-tubocurarine, as compared to free-moving animals, were used, it appears that, as observed with apomorphine, the effects of TRH on cerebellar cGMP are significantly reduced, indicating that increased motor activity contributes to the elevated cyclic nucleotide levels after this peptide (Lundberg et al., 1979).

4. Cholecystokinin receptor modulators. There are currently two major CCK receptor subtypes. The CCK-A, or peripheral type, CCK receptor has high affinity only for the sulfated forms of CCK which are 8 amino acids

or more (reviewed by Wood et al., 1988b); this receptor subtype is also present in the brain. Proglumide and CR-1409 are antagonists of this receptor subtype. The CCK-B, or brain, receptor is less discriminatory in that it also has high affinity for CCK-4 and unsulfated forms of the larger peptide fragments (Wood et al., 1988b; Wood, 1989).

Initial observations that parenteral administration of CCK would antagonize the tremorogenic effects of harmaline (Zettler, 1983) led to the evaluation of CCK analogues on cerebellar cGMP levels (Wood et al., 1988b). CCK-8 sulfate, CCK-8 unsulfated, and CCK-4 all dose dependently decreased basal cerebellar cGMP levels, suggesting activity at the CCK-B type receptor. This conclusion was supported by the inability of proglumide or CR 1409 to antagonize the effects on cGMP levels. No opioid involvement was suggested, because naloxone pretreatment did not modify the effects of CCK (Wood et al., 1988b).

The effects of CCK-8 sulfate on cGMP levels, augmented by various stimulants, were also investigated (Wood et al., 1988b; Wood, 1989). Pretreatments with CCK were found to antagonize the effects of dopaminergic (amphetamine, apomorphine, DN-1417) and cholinergic (oxotremorine) mossy fiber stimulation, as well as climbing fiber activation by harmaline. This modulation was not a local cerebellar effect as reflected by lack of activity after direct intracerebellar injections of CCK (201). These data, therefore, argue in favor of an extracerebellar modulation of both climbing and mossy fiber input to the cerebellum by CCK. In support of this hypothesis, CCK was found not to alter the effects of the intracerebellar convulsants, pentylenetetrazol and picrotoxin.

Caerulein, a peptide chemically related to CCK and isolated from frog skin, also antagonizes harmaline-dependent tremor (Zettler, 1983) and antagonizes harmaline-dependent increases in cerebellar cGMP (Kageyama and Kurosawa, 1989). In contrast, this peptide did not antagonize apomorphine- or methamphetamine-dependent increases in cerebellar cGMP (Kageyama and Kurosawa, 1989). Additionally, the effects of this peptide were blocked by vagotomy, suggesting a peripheral locus of action. The differences observed for this peptide may well relate to a species difference because caerulein was studied in rats and the CCK studies were performed in mice. Another clear difference was the duration of effect; caerulein antagonized the effects of harmaline up to 30 h postinjection in the rat, long after the peptide had been degraded, whereas CCK only antagonized the effects of harmaline up to 1 h in the mouse. These data argue for a long-term adaptive mechanism in the actions of caerulein in the rat.

5. Opiates. Morphine has been shown to dose and time dependently decrease cerebellar cGMP levels in the rat (Biggio et al., 1977b; Katz and Catravas, 1976). These actions were stereospecific as assessed with the stereoisomers of the opiate agonist viminol (Biggio et al., 1977b). The opiate receptor antagonist, naltrexone, did not alter basal cGMP levels but did antagonize the deceases elicited by opiate agonists (Biggio et al., 1977b). Naloxone, at opioid receptor antagonist doses, also did not alter basal cerebellar cGMP levels; however, at extremely high doses (60–240 mg/kg) this drug elicited dose-dependent increases in cGMP, presumably via a GABA-antagonist action (Gumulka et al., 1979b).

The actions of morphine were not altered by 3-acetylpyridine lesions of the climbing fibers (Biggio et al., 1977d), were not reproduced by direct intracerebellar injections (Biggio et al., 1977b,d), but were reproduced by intrastriatal injections (Biggio et al., 1977b,d). These data are consistent with a modulatory effect of striatal opioid synapses on the striatal output neurons which modulate pontocerebellar mossy fiber input to the cerebellum (fig. 4; section V.B.1). This conclusion is further supported by the report (Biggio et al., 1978c) of dose-dependent decreases in cerebellar cGMP by intrastriatal injections of the enkephalin analogue, D-Ala_2-Met-enkephalinamide. As with morphine, the actions of this peptide derivative were reversed by the opiate antagonist naltrexone and were not replicated by direct intracerebellar administration (Biggio et al., 1978c).

In mice, strain differences in the actions of morphine on cerebellar cGMP have been reported, with increases in some strains and decreases in others (Askew and Charalampous, 1976; Racagni et al., 1979). These differences may well reflect strain differences in the effects of morphine on dopamine release within the striatum (Wood and Altar, 1989; Wood and Richard, 1982; Wood, 1983) because C57BL/6J mice had parallel increases in striatal dopamine release, increased cerebellar cGMP, and enhanced motor activity, whereas DBA mice had decrements in striatal dopamine release and cerebellar cGMP with no change in motor activity (Racagni et al., 1979).

During withdrawal, morphine-dependent rats possess elevated basal cerebellar cGMP levels and are more sensitive to apomorphine-dependent increases in cGMP levels (Volicer et al., 1977), again supporting an opioid-dopamine linkage in the striato-pontocerebellar mossy fiber pathway (fig. 4).

6. Indole modulators. The cerebellum receives extensive serotonergic innervation from the raphe (Palay and Chan-Palay, 1974); however, a comprehensive study of serotonin receptor agonists and antagonists, for their effects on cerebellar cGMP, has never been undertaken.

The serotonin uptake inhibitor, fluoxetine, and the serotonin precursor, 5-hydroxytryptophan, did not alter basal cGMP levels (Chung, 1983). The nonselective and nonspecific serotonin agonists lysergic acid (Burkard et al., 1976) and 5-methoxy-dimethyl-tryptamine (Lykouras et al., 1980) increased cGMP levels; however, the

receptor type involved in this action is not known. In the case of lysergic acid, the increases in cGMP were counteracted by the neuroleptic, haloperidol, suggesting possible dopaminergic involvement (Burkard et al., 1976) while those of 5-methoxy-dimethyl-tryptamine were not blocked by haloperidol, cyproheptadine, or methysergide (Lykouras et al., 1980). The serotonin antagonists, cinnanserin (Chung, 1983) and cyproheptadine (Dinnendahl and Gumulka, 1977), did not alter basal cGMP levels in the cerebellum.

In summary, little is known of the serotonergic modulation of cerebellar cGMP levels; however, with the wealth of new pharmacological tools for serotonergic receptor subtypes, our knowledge in this area will undoubtedly increase.

7. Noradrenergic modulators. The cerebellum also receives extensive noradrenergic innervation from the locus coereleus (Bloom et al., 1971; Olsen and Fuxe, 1971). Studies of the β-adrenergic agonist, isoproterenol (Haidamous et al., 1980), and the β-adrenergic antagonist, propranolol (Dinnendahl and Gumulka, 1977; Narumi et al., 1983), have shown no changes in basal cerebellar cGMP levels.

In contrast, the α_1-adrenergic agonists, methoxamine and phenylephrine, increased cerebellar cGMP levels, as did intraventricular administration of norepinephrine itself (Haidamous et al., 1980). The α_2 agonist clonidine decreased cerebellar cGMP (Haidamous et al., 1980). Similarly, the α_1 antagonists phenoxybenzamine (Chung, 1983; Haidamous et al., 1980) and phentolamine (Haidamous et al., 1980) decreased cGMP in the rat cerebellum. However, phentolamine has been reported not to alter cGMP in the mouse cerebellum (Dinnendahl and Gumulka, 1977).

The α_2 antagonist, yohimbine, and the mixed α_1/α_2 antagonist, piperoxan, did not alter cGMP levels in the cerebellum (Haidamous et al., 1980).

In toto, it appears from these studies that a noradrenergic fiber input to the cerebellum innervates α_1-adrenergic receptors which, when activated, augment cerebellar cGMP content. Some data also suggest that there may be a basal ongoing tone to this noradrenergic input. Consistent with these data are observations that NMDA augments norepinephrine release from cerebellar slices, actions blocked both by competitive and noncompetitive NMDA receptor antagonists (Yi et al., 1988). An extension of these data are the observations that the nonselective α_1 antagonist, clozapine, and the selective α_1 antagonist, WB-4101, both block increases in cerebellar cGMP, in vivo, induced by NMDA receptor activation but not quisqualate receptor activation (Rao et al., 1990i; Wood and Rao, 1990; section III.B.6). These data are all consistent with a presynaptic NMDA receptor regulating norepinephrine release from noradrenergic fiber inputs to the cerebellum.

VI. Miscellaneous Pharmacological Agents

A number of miscellaneous pharmacological agents have been studied for their effects on cerebellar cGMP levels. These compounds include the antihistaminics, diphenhydramine and antazoline, which were inactive (Dinnendahl and Gumulka, 1977); the prostaglandin synthetase inhibitor, indomethacin, which was inactive (Dinnendahl and Gumulka, 1977; Mao et al. 1974a); and atrial naturistic factor which increased cGMP levels in granule cell cultures (Hoffman et al., 1989b) and in vivo after intracerebellar administration (P. L. Wood, unpublished observations).

VII. Conclusions

From the great array of pharmacological data presented in this review can be distilled several key features of the transduction mechanisms modulating cerebellar cGMP levels. The EAA pathways within and afferent to the cerebellum are key focal points receiving inputs from dopaminergic, cholinergic, and peptidergic neuronal projections. The EAA receptor subtype involved in vivo in the postsynaptic transduction of these diverse inputs to EAA-utilizing pathways appears mainly to involve NMDA-type EAA receptors. This hypothesis comes from the observations that competitive NMDA antagonists block locomotor-dependent increases in cGMP (McCaslin and Morgan, 1986b,c) and block increases in cGMP elicited by pharmacological potentiation of endogenous EAA release by climbing fiber activation with harmaline (Wood et al., 1982, 1989c,d, 1990a,b), activation of mossy fibers with oxotremorine (Wood et al., 1982), or removal of inhibitory GABAergic inputs with pentylenetetrazol (Ferrendelli et al., 1980; Wood et al., 1990a). The anatomical locus of NMDA actions also appears to be very specific in that the major portion of NMDA effects on cerebellar cGMP appear to be mediated by modulation of cerebellar norepinephrine release (Marwaha et al., 1980; 1981; Rao et al., 1990h; Wood and Rao, 1990). These effects appear to be finally dependent upon α_1 receptor activation of postsynaptic neurons (fig. 5); the residual (20–30%) activity of NMDA on cGMP levels remaining after α_1 blockade presumably involves NMDA activation of receptors on granule cells (fig. 5; Favaron et al., 1988; Novelli et al., 1987; Wrobleweski et al., 1987).

The other general feature of this system is that augmentation of cerebellar cGMP by EAA receptors and, therefore, all afferents acting through EAA pathways involves prior synthesis of NO. This generation of NO by EAA receptor-bearing neurons leads to a tremendous amplification system in that NO can diffuse to a wide diversity of neuronal and glial cell types as well as nerve terminals where it stimulates guanylate cyclase to generate cGMP (fig. 5). The diverse targets where cGMP then acts remain to be defined; however, the diversity of cGMP protein kinases present in the cerebellum (Schli-

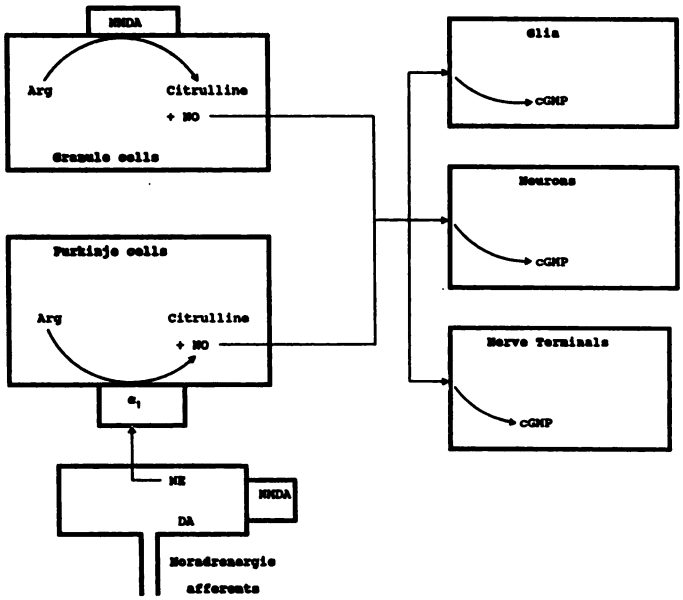

FIG. 5. Proposed scheme for the NMDA augmentation of NO synthase activity in granule and Purkinje cell populations with a resultant activation of guanylate cyclase and cGMP synthesis in diverse cell populations after diffusion of NO. In the case of Purkinje cells, the NMDA modulation appears to be indirect via effecting norepinephrine release first. Arg, arginine; DA, dopamine; NE, norepinephrine.

chter et al., 1980) offers targets worthy of study. Additionally the subsequent steps leading to induction of nuclear protooncogenes, such as c-*fos*, require clearer definition (Szekely et al., 1989).

As a large number of positive regulatory inputs appear to act via EAA-utilizing synapses to augment cerebellar cGMP, a number of inhibitory influences appear to act via inhibitory GABAergic interneurons in the cerebellum (Biggio et al., 1977a,d; Mohler et al., 1981). A notable exception to this is the depressant actions of ethanol that are mediated by NMDA receptor antagonism (Hoffman et al., 1989a,b).

In summary, the neuronal activity of the cerebellum involves a delicate balance between EAA and GABAergic neurons, both possessing extensive and diverse synaptic inputs. The actions of these two major neurotransmitter systems have been extensively characterized at the receptor level, and as presented in this review, our knowledge of subsequent signal transduction steps is increasing.

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