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# **PHARMACOLOGICAL REVIEWS**<br> **PHARMACOLOGICAL REVIEWS**<br> **Pharmacology of the Second Messenger, Cyclic**<br> **Guanosine 3',5'-Monophosphate, in the Cerebellum GUANOSI (ASSOLUTER)**<br>
COLOGICAL REVIEWS<br>
The American Society for Pharmacology and Experimental Therapeutics<br> **Guanosine 3',5'-Monophosphate, in the Cerebellum**<br>
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# I. Introduction

THE cyclic nucleotide cGMP† has been demonstrated<br>to be an intracellular second messenger system within **1. Introduction** et<br>
THE cyclic nucleotide cGMP† has been demonstrated<br>
to be an intracellular second messenger system within<br>
the cerebellum. High concentrations of cGMP (Chan-I. Introduction<br>THE cyclic nucleotide cGMP† has been demonstrat<br>to be an intracellular second messenger system with<br>the cerebellum. High concentrations of cGMP (Chan-<br>Palay and Palay, 1979; Rubin and Ferrendelli, 19 THE cyclic nucleotide cGMP† has been demonstrated<br>to be an intracellular second messenger system within<br>the cerebellum. High concentrations of cGMP (Chan-<br>Palay and Palay, 1979; Rubin and Ferrendelli, 1977;<br>Steiner et al., THE cyclic nucleotide cGMP† has been demonstrated<br>to be an intracellular second messenger system within<br>the cerebellum. High concentrations of cGMP (Chan-<br>Palay and Palay, 1979; Rubin and Ferrendelli, 1977;<br>Steiner et al. to be an intracellular second messenger system within<br>the cerebellum. High concentrations of cGMP (Chan-<br>Palay and Palay, 1979; Rubin and Ferrendelli, 1977;<br>Steiner et al., 1972; de Vente et al., 1989; Waldman and<br>Murad, the cerebellum. High concentrations of cGMP (Chan-<br>Palay and Palay, 1979; Rubin and Ferrendelli, 1977;<br>Steiner et al., 1972; de Vente et al., 1989; Waldman and<br>Murad, 1987), of the synthetic enzyme, guanylate cyclase<br>(Aria Palay and Palay, 1979; Rubin and Ferrendelli, 19<br>Steiner et al., 1972; de Vente et al., 1989; Waldman<br>Murad, 1987), of the synthetic enzyme, guanylate cycl<br>(Ariano et al., 1982; Waldman and Murad, 1987; Zwi<br>et al., 1981), Steiner et al., 1972; de Vente et al., 1989; Waldman and<br>Murad, 1987), of the synthetic enzyme, guanylate cyclase<br>(Ariano et al., 1982; Waldman and Murad, 1987; Zwiller<br>et al., 1981), of the degradative enzyme cGMP phospho Murad, 1987), of the synthetic enzyme, guanylate cycle (Ariano et al., 1982; Waldman and Murad, 1987; Zwillet al., 1981), of the degradative enzyme cGMP phosphetics.<br>Het al., 1981), of the degradative enzyme cGMP phospheti (Ariano et al., 1982; Waldman and Murad, 1987; Zwiller<br>et al., 1981), of the degradative enzyme cGMP phospho-<br>diesterase (Greenberg et al., 1978; Uzunov and Weiss,<br>1972), and of cGMP-dependent protein kinases (Schli-<br>chte diesterase (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 diesterase (Greenberg et al., 1978; Uzunov and Weiss<br>1972), and of cGMP-dependent protein kinases (Schlichter et al., 1980) have been found to be present in the<br>cerebellum. Additionally, there have been a large number<br>of p 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 cereb chter 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 ma 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 thi 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 continuity to critically assess our current interpretations bellar 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 tran chinery 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 for-<br>mat this review to critically assess our current interpretations and<br>of where this cGMP is generated and to examine the<br>transducer mechanisms that are coupled to cGMP for-<br>mation. The neurochemical anatomy of the cerebellar<br>c of where this cGMP is generated and to examine the transducer mechanisms that are coupled to cGMP for-<br>mation. The neurochemical anatomy of the cerebellar routine<br>circuits and their afferents also will be reviewed when<br>re mation. 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  $D$ .<br>
Merowave Tissue Fixation drug<br>
For rapid stabilization of postmortem changes in  $D$ .<br>
HMP levels, immersion in liquid nitrogen (Kimura et II. Methodology<br>A. Microwave Tissue Fixation<br>For rapid stabilization of postmortem changes in<br>cGMP levels, immersion in liquid nitrogen (Kimura et<br>al., 1974) or "nitrogen brain blowing" (Guidotti et al., A. Microwave Tissue Fixation<br>
For rapid stabilization of postmortem changes in<br>
cGMP levels, immersion in liquid nitrogen (Kimura et<br>
al., 1974) or "nitrogen brain blowing" (Guidotti et al.,<br>
1974) were first used. However 1974) were first used. However, these methods makes in  $D$ .<br>
1974) or "nitrogen brain blowing" (Guidotti et al.,  $D$ <br>
1974) were first used. However, these methods make fine<br>
1987) were first used. However, these methods For rapid stabilization of postmortem changes in cGMP levels, immersion in liquid nitrogen (Kimura e al., 1974) or "nitrogen brain blowing" (Guidotti et al. 1974) were first used. However, these methods make fine dissectio al., 1974) or "nitrogen brain blowing" (Guidotti et al.,  $P_U$ <br>1974) were first used. However, these methods make fine<br>dissection of brain regions difficult or impossible. Sub-<br>sequently, a number of laboratories demonstra 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 de 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., 19 sequently, a number of laboratories demonstrated<br>ease and utility of focused microwave fixation for<br>determination of cerebellar cGMP levels (Dodson et<br>1979; Guidotti et al., 1975; Jones and Stavinoha, 19<br>Mao et al., 1974b; **ease and utility of focused microwave fixation for the efficial determination of cerebellar cGMP levels (Dodson et al., pyrilies, 1979; Guidotti et al., 1975; Jones and Stavinoha, 1977; How Mao et al., 1974b; Wood et al.** determination of cerebellar cGMP levels (Dodson et al., p. 1979; Guidotti et al., 1975; Jones and Stavinoha, 1977; Mao et al., 1974b; Wood et al., 1982). In many laboratometries, this method of tissue fixation is highly a 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 prot ries, this method of tissue fixation is highly amenable to<br>subsequent microdissection of brain regions and yields<br>basal cGMP levels in the range of 1-3 pmol/mg protein.<br>B. Tissue Microdissection<br>Microdissection of the cere

bsequent microdissection of brain regions and yields<br>sal cGMP levels in the range of  $1-3$  pmol/mg protein.<br>Tissue Microdissection<br>Microdissection of the cerebellum involved dissection (<br>the cortex, vermis and deep cerebe basal cGMP levels in the range of 1-3 pmol/mg protein.<br>
B. Tissue Microdissection<br>
methodissection of the cerebellum involved dissection ("<br>
of the cortex, vermis and deep cerebellar nuclei (Biggio (tat<br>
tAbbreviations: c Microdissection of the cerebellum involved dissectively<br>the cortex, vermis and deep cerebellar nuclei (Big;<br>tAbbreviations: cGMP, cyclic guanosine 3',5'-monophosphand.

Microdissection of the cerebellum involved dissection<br>of the cortex, vermis and deep cerebellar nuclei (Biggio<br>tabbreviations: cGMP, cyclic guanosine 3',5'-monophosphate;<br>NMDA, N-methyl-D-aspartate; TRH, thyrotropin-releas of the cortex, vermis and deep cerebellar nuclei (Biggio (the cortex, cGMP, cyclic guanosine  $3',5'$ -monophosphate; NMDA, N-methyl-D-aspartate; TRH, thyrotropin-releasing hormone; GABA,  $\gamma$ -aminobutyric acid; EAA, excitat oxide; PCP, phencyclidine; CNS, central nervous system; CO-1996.<br>
NMDA, N-methyl-D-aspartate; TRH, thyrotropin-releasing hormon<br>
GABA,  $\gamma$ -aminobutyric acid; EAA, excitatory amino acid; NO, nitroxide; PCP, phencyclidine; †Abbreviations: cGMP, cyclic guanosine  $3',5'$ -monople NMDA, N-methyl-D-aspartate; TRH, thyrotropin-releasing IGABA,  $\gamma$ -aminobutyric acid; EAA, excitatory amino acid; Noride; PCP, phencyclidine; CNS, central nervous syst NMDA, N-methyl-D-aspartate; TRH, thyrotropin-releasing GABA,  $\gamma$ -aminobutyric acid; EAA, excitatory amino acid; Noride; PCP, phencyclidine; CNS, central nervous system; CC<br>cystokinin; DN-1417,  $\gamma$ -butyrolactone- $\gamma$ -carb acid.

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 et al., 1977a; Guidotti et al., 1975; Rubin and Ferrendelli,<br>1977). Of the drugs tested to date, parallel changes in<br>cGMP levels occurred in all 3 regions, except in the case et al., 1977a; Guidotti et al., 1975; Rubin and Ferrendelli,<br>1977). Of the drugs tested to date, parallel changes in<br>cGMP levels occurred in all 3 regions, except in the case<br>of muscarinic agonist administration, which inc of muscarinic agonist administration, which increased only vermal cGMP levels (Rubin and Ferrendelli, 1977). 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 inc 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). cGMP levels occurred in all 3 regions, except in the case<br>of muscarinic agonist administration, which increased<br>only vermal cGMP levels (Rubin and Ferrendelli, 1977).<br>Further microdissection of cell layers in the cerebellu of muscarinic agonist administration, which increased<br>only vermal cGMP levels (Rubin and Ferrendelli, 1977).<br>Further microdissection of cell layers in the cerebellum<br>indicated that generally 80% of the changes in cGMP<br>leve only vermal cGMP levels (Rubin and Ferrendelli, 1977).<br>Further microdissection of cell layers in the cerebellum<br>indicated that generally 80% of the changes in cGMP<br>levels occurs in the molecular layer and 20% in the<br>granul 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 det mot all drug effects have been monitored in such anatomical detail, indicating that this may not always be the case.<br> **C. Routes of Drug Administration**<br>
The in vivo evaluation of drug effects on cerebellar

Indicating that this may not always be the<br>se.<br>Routes of Drug Administration<br>The in vivo evaluation of drug effects on cerebellar<br>IMP is most often determined with parenteral drug case.<br>C. Routes of Drug Administration<br>The in vivo evaluation of drug effects on cerebellar<br>cGMP is most often determined with parenteral drug<br>administration. However, when drug bioavailability is an C. Routes of Drug Administration<br>The in vivo evaluation of drug effects on cerebellar<br>cGMP is most often determined with parenteral drug<br>administration. However, when drug bioavailability is an<br>issue or when the site(s) of C. *Routes of Drug Administration*<br>The in vivo evaluation of drug effects on cerebellar<br>cGMP is most often determined with parenteral drug<br>administration. However, when drug bioavailability is an<br>issue or when the site(s) The in vivo evaluation of drug effects on cerebellar<br>cGMP is most often determined with parenteral drug<br>administration. However, when drug bioavailability is an<br>issue or when the site(s) of drug action is being studied,<br>th cGMP is most often determined with parenteral drug<br>administration. However, when drug bioavailability is an<br>issue or when the site(s) of drug action is being studied,<br>then direct intracranial injections are performed. Thes 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., 1 issue or when the site(s) of drug action is being studied,<br>then direct intracranial injections are performed. These<br>routes include intraventricular (Danysz et al., 1989;<br>McCaslin and Morgan, 1986b), intracisternal (Wood et then direct intracranial injections are performed. These<br>routes include intraventricular (Danysz et al., 1989;<br>McCaslin and Morgan, 1986b), intracisternal (Wood et<br>al., 1982), and direct intracerebellar (Rao et al., 1990b, routes include intraventricular (Danysz et al., 1989;<br>McCaslin and Morgan, 1986b), intracisternal (Wood et<br>al, 1982), and direct intracerebellar (Rao et al., 1990b,c;<br>Wood et al., 1987, 1988b, 1989a,d, 1990a) injections. D 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 u Wood et al., 1987, 1988b, 1989a,d, 1990a) injections. Drug<br>injections into extracerebellar brain regions, from which<br>afferent pathways originate, have also been used to define<br>drug effects on cerebellar inputs (section V.B *afferent pathways originate, have also been used to define drug effects on cerebellar inputs (section V.B.1).*<br>*D. Lesions/Mutant Mice*<br>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 D. Lesions/Mutant Mice<br>The relative roles of afferent fiber pathways as well as<br>Purkinje and granule cell populations in cGMP re-<br>sponses to drug treatments have been investigated by the<br>use of both chemical lesions and ge D. Lesions/Mutant Mice<br>
The relative roles of afferent fiber pathways as well as<br>
Purkinje and granule cell populations in CGMP re-<br>
sponses to drug treatments have been investigated by the<br>
use of both chemical lesions an The relative roles of afferent fiber pathways as well as<br>Purkinje and granule cell populations in cGMP re-<br>sponses to drug treatments have been investigated by the<br>use of both chemical lesions and genetically mutant mice.<br> Purkinje and granule cell populations in cGMP<br>sponses to drug treatments have been investigated by<br>use of both chemical lesions and genetically mutant m<br>In the case of the climbing fiber system (section I<br>efficient lesions sponses to drug treatments have been investigated by the use of both chemical lesions and genetically mutant mice.<br>In the case of the climbing fiber system (section IV), efficient lesions can be obtained with the toxin 3-a use of both chemical lesions and genetically mutant mice.<br>In the case of the climbing fiber system (section IV),<br>efficient lesions can be obtained with the toxin 3-acetyl-<br>pyridine (Guidotti et al., 1975; McBride et al., 1 In the case of the climbing fiber system (section IV),<br>efficient lesions can be obtained with the toxin 3-acetyl-<br>pyridine (Guidotti et al., 1975; McBride et al., 1978).<br>However, although this lesion is easily created in r efficient lesions ca<br>pyridine (Guidott<br>However, although<br>our hands, this to<br>extremely lethal.<br>For the selectiv ridine (Guidotti et al., 1975; McBride et al., 1978)<br>owever, although this lesion is easily created in rats,<br>r hands, this toxin is not useful in mice because it<br>tremely lethal.<br>For the selective depletion of cell populati However, although this lesion is easily created in rats, in<br>our hands, this toxin is not useful in mice because it is<br>extremely lethal.<br>For the selective depletion of cell populations, virus-<br>induced granule cell loss in t

our hands, this toxin is not useful in mice because it is<br>extremely lethal.<br>For the selective depletion of cell populations, virus-<br>induced granule cell loss in the hamster cerebellum was<br>reported (Young et al., 1974). For extremely lethal.<br>For the selective depletion of cell populations, virus-<br>induced granule cell loss in the hamster cerebellum was<br>reported (Young et al., 1974). For mice, a number of<br>strains are available with selective lo For the selective depletion of cell populations, virus-<br>induced granule cell loss in the hamster cerebellum was<br>reported (Young et al., 1974). For mice, a number of<br>strains are available with selective losses of granule<br>(" induced gram<br>
reported (Y<br>
strains are<br>
("Weaver m<br>
(table 1).<br>
F G ( *Example 3* are available with selective losses of granule ("Weaver mouse") and Purkinje ("Nervous mouse") cells (table 1).<br> *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 (table 1).<br>
E. Confounding Variables<br>
1. Motor activity. The issue has been raised that many<br>
drug effects on cerebellar cGMP may result from changes<br>
in the motor state of an animal. The basis for this E. Confounding Variables<br>1. Motor activity. The issue has been raised that many<br>drug effects on cerebellar cGMP may result from changes<br>in the motor state of an animal. The basis for this<br>hypothesis was the observation of E. Confounding variables<br>1. Motor activity. The issue has been raised that many<br>drug effects on cerebellar cGMP may result from changes<br>in the motor state of an animal. The basis for this<br>hypothesis was the observation of

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cGMP levels in the cerebella of rats trained to run in an cGMP is not increased by all agents that potentiate<br>activity wheel (Meyerhoff et al., 1979). Similarly, rats dopaminergic transmission and increase motor activity Guanylate cyclase Normal<br>
CGMP levels in the cerebella of rats trained to run in an<br>
activity wheel (Meyerhoff et al., 1979). Similarly, rats<br>
trained to swim a 2.5-m course possessed elevated cerecGMP levels in the cerebella of rats trained to run in a<br>activity wheel (Meyerhoff et al., 1979). Similarly, rat<br>trained to swim a 2.5-m course possessed elevated cere<br>bellar cGMP levels; this effect was blocked by competi cGMP levels in the cerebella of rats trained to run in<br>activity wheel (Meyerhoff et al., 1979). Similarly, 1<br>trained to swim a 2.5-m course possessed elevated ce<br>bellar cGMP levels; this effect was blocked by comp<br>tive NMD cGMP levels in the cerebella of rats trained to run in an cGlackivity wheel (Meyerhoff et al., 1979). Similarly, rats doptrained to swim a 2.5-m course possessed elevated cere-<br>bellar cGMP levels; this effect was blocked b activity wheel (Meyerhoff et al., 1979). Similarly, rats<br>trained to swim a 2.5-m course possessed elevated cere-<br>bellar cGMP levels; this effect was blocked by competi-<br>tive NMDA (section III.A) antagonists (McCaslin and<br>M trained to swim a 2.5-m course possessed elevated cerebreals bellar cGMP levels; this effect was blocked by competitive NMDA (section III.A) antagonists (McCaslin and dMorgan, 1986a–c). Pharmacological studies using motor bellar 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 tive NMDA (section III.A) antagonists (McCaslin and<br>Morgan, 1986a–c). Pharmacological studies using motor<br>stimulants also have demonstrated a role for an enhanced<br>motor activity in the increases in cerebellar cGMP in-<br>duce Morgan, 1986a–c). Pharmacological studies using motor the stimulants also have demonstrated a role for an enhanced expotor activity in the increases in cerebellar cGMP included by both apomorphine and TRH (section V.B.3) stimulants also have demonstrated a role for an enhanced<br>motor activity in the increases in cerebellar cGMP in-<br>duced by both apomorphine and TRH (section V.B.3)<br>but not by harmaline (Lundberg et al., 1979). In these<br>studi motor activity in the increases in cerebellar cGMP in-<br>duced by both apomorphine and TRH (section V.B.3) n<br>but not by harmaline (Lundberg et al., 1979). In these p<br>studies, the effects of TRH and apomorphine were sig-<br>nifi duced by both apomorphine and TRH (section V.B<br>but not by harmaline (Lundberg et al., 1979). In the<br>studies, the effects of TRH and apomorphine were s<br>nificantly attenuated, but not absent, in rats paralyz<br>with *d*-tubocur but not by harmaline (Lundberg et al., 1979). In these plat studies, the effects of TRH and apomorphine were sig-<br>nificantly attenuated, but not absent, in rats paralyzed return of a berg et al., 1979). In paralyzed animal studies, the effects of TRH and apomorphine were significantly attenuated, but not absent, in rats paralyze<br>with *d*-tubocurarine and mechanically ventilated (Lund<br>berg et al., 1979). In paralyzed animals, the decreases is mificantly attenuated, but not absent, in rats paralyze<br>with d-tubocurarine and mechanically ventilated (Lund<br>berg et al., 1979). In paralyzed animals, the decreases i:<br>GMP induced by the depressants pentobarbital, halo<br>th th *d*-tubocurarine and mechanically ventilated (Lund-<br>rg et al., 1979). In paralyzed animals, the decreases in THOF induced by the depressants pentobarbital, halo-<br>ane, and ethanol were also reduced (section III.B.5). 19

berg et al., 1979). In paralyzed animals, the decreases in cGMP induced by the depressants pentobarbital, halo-<br>thane, and ethanol were also reduced (section III.B.5).<br>Thus, it appears that enhanced motor activity can<br>resu cGMP induced by the depressants pentobarbital, halo-<br>thane, and ethanol were also reduced (section III.B.5).<br>Thus, it appears that enhanced motor activity can<br>result in increased cerebellar cGMP levels and vice versa.<br>Howe thane, and ethanol were also reduced (section III.B.5).<br>Thus, it appears that enhanced motor activity ca<br>result in increased cerebellar cGMP levels and vice verse<br>However, these parameters are not strictly correlated<br>the r Thus, it appears that enhanced motor activity c<br>result in increased cerebellar cGMP levels and vice ver<br>However, these parameters are not strictly correlat<br>the recovery of locomotor activity after pentobarbi<br>treatment is 3 result in increased cerebellar cGMP levels and vice versa.<br>However, these parameters are not strictly correlated:<br>the recovery of locomotor activity after pentobarbital<br>treatment is 30–60 min, whereas the recovery of cereb result in increased cerebellar cGMP levels and vice versa.<br>
However, these parameters are not strictly correlated:<br>
the recovery of locomotor activity after pentobarbital<br>
treatment is 30–60 min, whereas the recovery of ce the recovery of locomotor activity after pentobarbital<br>treatment is 30–60 min, whereas the recovery of cerebel-<br>lar cGMP levels is 120–150 min (Morgan and Pfeil, 1984;<br>section III.B.5); genetically dystonic rats which have treatment is 30–60 min, whereas the recovery of cerebellar cGMP levels is 120–150 min (Morgan and Pfeil, 1984;<br>section III.B.5); genetically dystonic rats which have<br>normal motor activity patterns possess cerebellar cGMP<br>l lar cGMP levels is 120–150 min (Morgan and Pfeil, 1984;<br>section III.B.5); genetically dystonic rats which have<br>normal motor activity patterns possess cerebellar cGMP<br>levels that are 33% of that of control rats (Lorden et a 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 incre normal motor activity patterns possess cerebellar cGMP in levels that are 33% of that of control rats (Lorden et al., in 1985); whereas C57Bl/6J mice have concomitant increases in motor activity and cerebellar cGMP levels 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 cerebell 1985); whereas C57Bl/6J mice have concomitant increases in motor activity and cerebellar cGMP levels<br>after morphine treatment and DBA mice have decreased<br>cerebellar cGMP in the absence of changes in motor<br>activity (Racagni

*by* (Racagni et al., 1979; section V.B.5); cerebe.<br> *after treatment with dopaminergics (Breese et al., 1979a)*<br> **after treatment with dopaminergics (Breese et al., 1979a)** 

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	$10.7*$	$3.18*$	

 $* p < 0.05$ .

Schmidt and Nadi, 1977<br>CGMP is not increased by all agents that potentiate<br>dopaminergic transmission and increase motor activity<br>(Breese et al., 1979a; section V.B.1; table 2). eGMP is not increased by all agents that proportions and increase moto<br>(Breese et al., 1979a; section V.B.1; table 2).<br>2. Stress. A further complication in the art <sup>2</sup> AMP is not increased by all agents that potentiate paminergic transmission and increase motor activity irreese et al., 1979a; section V.B.1; table 2).<br>2. *Stress.* A further complication in the analysis of ug and behav cGMP is not increased by all agents that potentiate<br>dopaminergic transmission and increase motor activity<br>(Breese et al., 1979a; section V.B.1; table 2).<br>2. Stress. A further complication in the analysis of<br>drug and behavi

dopaminergic transmission and increase motor activity<br>
(Breese et al., 1979a; section V.B.1; table 2).<br>
2. Stress. A further complication in the analysis of<br>
drug and behavioral effects on cerebellar cGMP levels is<br>
the po (Breese et al., 1979a; section V.B.1; table 2).<br>
2. Stress. A further complication in the analysis of<br>
drug and behavioral effects on cerebellar cGMP levels is<br>
the potential for a significant stress component in any<br>
expe 2. Stress. A further complication in the analysis drug and behavioral effects on cerebellar cGMP levels is the potential for a significant stress component in an experimental paradigm. Indeed, elevated cerebellar cGMP leve drug and behavioral effects on cerebellar cGMP levels is<br>the potential for a significant stress component in any<br>experimental paradigm. Indeed, elevated cerebellar<br>cGMP levels have been measured in fighting mice (Din-<br>nend the potential for a significant stress component in any<br>experimental paradigm. Indeed, elevated cerebellar<br>cGMP levels have been measured in fighting mice (Din-<br>nendahl, 1975), in mice stressed in ice water or on a hot<br>pl experimental paradigm. Indeed, elevated cerebellar<br>cGMP levels have been measured in fighting mice (Din-<br>nendahl, 1975), in mice stressed in ice water or on a hot<br>plate (Dinnendahl, 1975), and in rats maintained at 4°C<br>(Ma cGMP levels have been measured in fighting mice (Din-<br>nendahl, 1975), in mice stressed in ice water or on a hot<br>plate (Dinnendahl, 1975), and in rats maintained at 4°C<br>(Mao et al., 1974a). In all cases, these elevations i plate (Dinnendahl, 1975), and in 1<br>(Mao et al., 1974a). In all cases, the<br>returned to normal between 15 and<br>of acute or chronic stress exposure.<br>The pharmacology of stress-inc (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.<br>The pharmacology of stress-induced cGMP increases also has been inv

(Mao et al., 1974a). In all cases, these elevations in cGMP<br>returned to normal between 15 and 30 min after cessation<br>of acute or chronic stress exposure.<br>The pharmacology of stress-induced cGMP increases<br>also has been inve returned to normal between 15 and 30 min after cessation<br>of acute or chronic stress exposure.<br>The pharmacology of stress-induced cGMP increases<br>also has been investigated (Dinnendahl and Gumulka,<br>1977). These increases are of acute or chronic stress exposure.<br>The pharmacology of stress-induced cGMP increase<br>also has been investigated (Dinnendahl and Gumulka<br>1977). These increases are blocked by pretreatment with<br>pentobarbital, diazepam, chlo The pharmacology of stress-induced cGMP increases<br>also has been investigated (Dinnendahl and Gumulka,<br>1977). These increases are blocked by pretreatment with<br>pentobarbital, diazepam, chlorpromazine, haloperidol,<br>aminooxyac also has been investigated (Dinnendahl and Gumulka,<br>1977). These increases are blocked by pretreatment with<br>pentobarbital, diazepam, chlorpromazine, haloperidol,<br>aminooxyacetic acid, reserpine, clonidine, and high doses<br>of 1977). These increases are blocked by pretreatment with pentobarbital, diazepam, chlorpromazine, haloperido aminooxyacetic acid, reserpine, clonidine, and high dose of propranolol (no stereospecificity). In contrast, acut pentobarbital, diazepam, chlorpromazine, haloperid<br>aminooxyacetic acid, reserpine, clonidine, and high dos<br>of propranolol (no stereospecificity). In contrast, acu<br>stress effects on cGMP were not altered by pretreatme<br>with aminooxyacetic acid, reserpine, clonidine, and high doses<br>of propranolol (no stereospecificity). In contrast, acute<br>stress effects on cGMP were not altered by pretreatment<br>with phentolamine, atropine, diphenhydramine, cypr of propranolol (no stereospecificity). In contrast, ac<br>stress effects on cGMP were not altered by pretreatm<br>with phentolamine, atropine, diphenhydramine, cyp<br>heptadine, or indomethacin (Dinnendahl and Gumul<br>1977). These da stress effects on cGMP were not altered by pretreatme<br>with phentolamine, atropine, diphenhydramine, cypi<br>heptadine, or indomethacin (Dinnendahl and Gumull<br>1977). These data lead to the conclusion that dopar<br>nergic and GABA induced increases in cerebellar cGMP (Wood et al., 1984a), whereas noradrenergic, serotonergic, histaminheptadine, or indomethacin (Dinnendahl and Gumu<br>1977). These data lead to the conclusion that dopa<br>nergic and GABAergic pathways are involved in str<br>induced increases in cerebellar cGMP (Wood et<br>1984a), whereas noradrenerg 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 cho nergic and GABAergic pathways are involved in stress-<br>induced increases in cerebellar cGMP (Wood et al.,<br>1984a), whereas noradrenergic, serotonergic, histamin-<br>ergic, and cholinergic pathways are not. Additionally,<br>enhance induced increases in cerebellar cGMP<br>1984a), whereas noradrenergic, serotone<br>ergic, and cholinergic pathways are no<br>enhanced prostaglandin synthesis is not<br>the cascade leading to increased cGMP.<br>The role of dopaminergic an 84a), whereas noradrenergic, serotonergic, histamin-<br>gic, and cholinergic pathways are not. Additionally,<br>hanced prostaglandin synthesis is not a component of<br>e cascade leading to increased cGMP.<br>The role of dopaminergic a enhanced prostaglandin synthesis is not a component of<br>the cascade leading to increased cGMP.<br>The role of dopaminergic and GABAergic pathways in<br>stress-induced cerebellar cGMP increases is further re-

activity (Racagni et al., 1979; section V.B.5); cerebellar<br>
The role of dopaminergic and GABAergic pathways in<br>
TABLE 2<br>
Lack of correlation of changes in motor activity and cerebellar cGMP<br>
after treatment with dopaminerg ergic, and cholinergic pathways are not. Additionally,<br>enhanced prostaglandin synthesis is not a component of<br>the cascade leading to increased cGMP.<br>The role of dopaminergic and GABAergic pathways in<br>stress-induced cerebel the cascade leading to increased cGMP.<br>The role of dopaminergic and GABAergic pathways in<br>stress-induced cerebellar cGMP increases is further re-<br>flected by studies of rats habituated to handling (Corda<br>et al., 1980). In t The role of dopaminergic and GABAergic pathways in<br>stress-induced cerebellar cGMP increases is further re-<br>flected by studies of rats habituated to handling (Corda<br>et al., 1980). In these animals, the basal cerebellar cGMP stress-induced cerebellar cGMP increases is further reflected by studies of rats habituated to handling (Corde<br>et al., 1980). In these animals, the basal cerebellar cGME<br>levels were 30% of naive rats and could not be furth flected 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 (s et al., 1980). In these animals, the basal cerebellar cGMP<br>levels were 30% of naive rats and could not be further<br>decreased by the dopamine antagonist haloperidol (sec-<br>tion V.B.1) or the GABAergics diazepam and muscimol<br>( 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 habituat decreased by the dopamine antagonist halop<br>tion V.B.1) or the GABAergics diazepam and<br>(section III.B.1). In contrast, apomorphin<br>V.B.1) still increased cerebellar cGMP in the<br>habituated to handling (Corda et al., 1980).<br>3. by V.B.1) or the GABAergics diazepam and muscimol<br>action III.B.1). In contrast, apomorphine (section<br>B.1) still increased cerebellar cGMP in these animals<br>bituated to handling (Corda et al., 1980).<br>3. Respiratory depressio (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).<br>3. Respiratory depression. It has been demonstrated in rats paralyz

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For depression should interpret their data with some actuation.<br>
The study of cerebellar cGMP levels in vivo offers the some<br>
tential to determine drug effects on cerebellar afferent au caution.<br>
F. In Vitro Studies<br>
The study of cerebellar cGMP levels in vivo offers the<br>
potential to determine drug effects on cerebellar afferent<br>
pathways, to examine drug effects in the presence of in F. In Vitro Studies<br>
The study of cerebellar cGMP levels in vivo offers the<br>
potential to determine drug effects on cerebellar afferent<br>
pathways, to examine drug effects in the presence of in<br>
vivo neuronal firing pattern F. In vitro studies<br>The study of cerebellar cGMP levels in vivo offers the<br>potential to determine drug effects on cerebellar afferent<br>pathways, to examine drug effects in the presence of in<br>wivo neuronal firing patterns, The study of cerebellar cGMP levels in vivo offers the<br>potential to determine drug effects on cerebellar afferent<br>pathways, to examine drug effects in the presence of in<br>wivo neuronal firing patterns, and to determine dru potential to determine drug effects on cerebellar afferent<br>pathways, to examine drug effects in the presence of in<br>vivo neuronal firing patterns, and to determine drug<br>bioavailability. However, when the purpose of a study pathways, to examine drug effects in the presence of in Her<br>vivo neuronal firing patterns, and to determine drug has<br>bioavailability. However, when the purpose of a study is<br>trance define mechanism(s) and site(s) of actio vivo neuronal firing patterns, and to determine drug has<br>bioavailability. However, when the purpose of a study is tra<br>to define mechanism(s) and site(s) of action of a drug, 198<br>investigators often integrate such in vivo bioavailability. Howev<br>to define mechanism<br>investigators often int<br>vitro evaluations in w<br>more easily regulated.<br>1. Cerebellar slices. define mechanism(s) and site(s) of action of a drug,  $1$ <br>vestigators often integrate such in vivo studies with in<br>oro evaluations in which experimental variables can be<br>ore easily regulated.<br>*1. Cerebellar slices*. Studie

investigators often integrate such in vivo studies with in vitro evaluations in which experimental variables can b<br>more easily regulated.<br>1. Cerebellar slices. Studies of tissue slices obtainee<br>from immature rat brain have vitro evaluations in which experimental variables can be<br>
more easily regulated.  $\begin{array}{c} \text{G} \\ \text{I} \end{array}$ . Cerebellar slices. Studies of tissue slices obtained<br>
from immature rat brain have demonstrated that cere-<br>
bella more easily regulated. GA<br>
1. Cerebellar slices. Studies of tissue slices obtained<br>
from immature rat brain have demonstrated that cere-<br>
bellar slices generate the greatest concentration of<br>
cGMP, paralleling in vivo obs 1. Cerebellar slices. Studies of tissue slices obtained 11<br>from immature rat brain have demonstrated that cere-<br>bellar slices generate the greatest concentration of<br>cGMP, paralleling in vivo observations (Palmer and<br>Duszy from immature rat brain have demonstrated that cere-<br>bellar slices generate the greatest concentration of<br>cGMP, paralleling in vivo observations (Palmer and<br>Duszynski, 1975). The higher levels of cGMP in this<br>hrain region bellar 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 phosphodie 1978). Duszynski, 1975). The higher levels of cGMP in this<br>brain region appear to result from lower levels of cGMP<br>phosphodiesterase in the cerebellum (Greenberg et al.,<br>1978).<br>A number of investigators have investigated the ac-<br>

brain region appear to result from lower levels of cGM<br>phosphodiesterase in the cerebellum (Greenberg et a<br>1978).<br>A number of investigators have investigated the a<br>tions of EAA agonists (section III.B.6) on cGMP gener-<br>ati phosphodiesterase in the cerebellum (Greenberg et al., 1978).<br>
A number of investigators have investigated the ac-<br>
tions of EAA agonists (section III.B.6) on cGMP gener-<br>
ation in cerebellar slices (Garthwaite and Brodbel 1978).<br>
A number of investigators have investigated the ac-<br>
tions of EAA agonists (section III.B.6) on cGMP gener-<br>
ation in cerebellar slices (Garthwaite and Brodbelt, 1989;<br>
Garthwaite, 1982; Schmidt and Nadi, 1977; Sc A number of investigators have investigated the<br>tions of EAA agonists (section III.B.6) on cGMP gen<br>ation in cerebellar slices (Garthwaite and Brodbelt, 19<br>Garthwaite, 1982; Schmidt and Nadi, 1977; Schmidt<br>al., 1977). Thes tions of EAA agonists (section III.B.6) on cGMP generation in cerebellar slices (Garthwaite and Brodbelt, 1989;<br>Garthwaite, 1982; Schmidt and Nadi, 1977; Schmidt et al., 1977). These studies demonstrated positive modulati ation in cerebellar slices (Garthwaite and Brodbelt, 1989;<br>Garthwaite, 1982; Schmidt and Nadi, 1977; Schmidt et<br>al., 1977). These studies demonstrated positive modula-<br>tion by kainate; however, the buffers used in these st 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 rece 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, modu tion by kainate; however, the buffers used in these studies<br>all contained  $Mg^{2+}$ , an antagonist of the NMDA receptor<br>complex (Ascher et al., 1988). As a result, modulation of<br>GGMP by NMDA was only weakly demonstrated or all contained Mg<sup>2+</sup>, an antagonist of the NMDA receptor<br>complex (Ascher et al., 1988). As a result, modulation of<br>cGMP by NMDA was only weakly demonstrated or not<br>demonstrated, whereas, indeed, there is such modulation<br>i 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 c cGMP by NMDA was only weakly demonstrated or not<br>demonstrated, whereas, indeed, there is such modulation<br>in vivo (III.B.6). Using a number of chemical lesions of<br>cell types in these slices, investigators concluded that the demonstrated, whereas, indeed, there is such modulation<br>in vivo (III.B.6). Using a number of chemical lesions of<br>cell types in these slices, investigators concluded that the<br>major cells initiating cGMP accumulation include 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 cell cell types in these slices, investigators concluded that<br>major cells initiating cGMP accumulation include<br>granule cells and astrocytes but not Purkinje<br>(Garthwaite and Brodbelt, 1989; Garthwaite, 1982); t<br>findings are in a major cells initiating c<br>granule cells and astr<br>(Garthwaite and Brodbe<br>findings are in agreem<br>studies (section III.A).<br>2. Cell fractions. Free 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).<br>2. *Cell fractions*. Freshly isolated (Garthwaite and Brodbelt, 1989; Garthwaite, 1982); these<br>findings are in agreement with immunohistochemical<br>studies (section III.A).<br>2. Cell fractions. Freshly isolated bulk cell fractions<br>obtained from immature rat cerebe

findings are in agreement with immunohistochemical<br>studies (section III.A).<br>2. Cell fractions. Freshly isolated bulk cell fractions<br>obtained from immature rat cerebellum (Gordon and<br>Balazs, 1983) have shown a rank order fo studies (section III.A).<br>2. Cell fractions. Freshly isolated bulk cell fractions<br>obtained from immature rat cerebellum (Gordon and<br>Balazs, 1983) have shown a rank order for guanylate<br>cyclase activity as follows (Bunn et al 2. Cell fractions. Freshly isolated bulk cell fractions obtained from immature rat cerebellum (Gordon and Garthwaite cyclase activity as follows (Bunn et al., 1986; Garthwaite and Garthwaite, 1987): glomerulus particles (m Balazs, 1983) have shown a rank order for guanylate<br>cyclase activity as follows (Bunn et al., 1986; Garthwaite<br>and Garthwaite, 1987): glomerulus particles (mossy ter-<br>minals + Golgi terminals + granule dendritic digits) ><br> cyclase activity as follows (Bunn et al., 1986; Garthwaite<br>
and Garthwaite, 1987): glomerulus particles (mossy ter-<br>
minals + Golgi terminals + granule dendritic digits) ><br>
astrocytes > Purkinje cells. Guanylate cyclase w and Garthwaite, 1987): glomoninals + Golgi terminals + astrocytes > Purkinje cells. (vated more than 10-fold in a prodrug, sodium nitroprussid 3. Cultured neurons. Culture inals + Golgi terminals + granule dendritic digits) incorptes > Purkinje cells. Guanylate cyclase was actived more than 10-fold in all cell fractions by the Nu odrug, sodium nitroprusside.<br>3. Cultured neurons. Cultures com

astrocytes > Purkinje cells. Guanylate cyclase was activated more than 10-fold in all cell fractions by the NO prodrug, sodium nitroprusside.<br>3. Cultured neurons. Cultures composed of  $>90\%$  granule cells can be obtained vated more than 10-fold in all cell fractions by the NO<br>prodrug, sodium nitroprusside.<br>3. Cultured neurons. Cultures composed of >90% gran-<br>ule cells can be obtained from a culture of immature rat<br>cerebellum (Drejer and S prodrug, sodium nitroprusside.<br>
3. Cultured neurons. Cultures composed of >90% que cells can be obtained from a culture of immature<br>
cerebellum (Drejer and Schousboe, 1989). These neu<br>
are EAA utilizing in that they demon 3. Cultured neurons. Cultures composed of  $>90\%$  gran-<br>ule cells can be obtained from a culture of immature rat<br>cerebellum (Drejer and Schousboe, 1989). These neurons<br>are EAA utilizing in that they demonstrate  $Ca^{2+}$ -de ule cells can be obtained from a culture of immature rat<br>cerebellum (Drejer and Schousboe, 1989). These neurons<br>are EAA utilizing in that they demonstrate Ca<sup>2+</sup>-depend-<br>ent glutamate release (Gallo et al., 1982; Levi et a

op<br>cells have shown NMDA- and kainate-dependent in-<br>creases in-CGMP, with concomitant increases in-Ca<sup>2</sup> D<br>cells have shown NMDA- and kainate-dependent in-<br>creases in CGMP, with concomitant increases in Ca<sup>2+</sup><br>uptake (Favaron et al., 1988; Novelli et al., 1987; Novelli uptake (Favaron NMDA- and kainate-dependent increases in cGMP, with concomitant increases in Ca<sup>2+</sup> uptake (Favaron et al., 1988; Novelli et al., 1987; Novelli and Henneberry, 1987; Wrobleweski et al., 1987). The cells have shown NMDA- and kainate-dependent in-<br>creases in cGMP, with concomitant increases in Ca<sup>2+</sup><br>uptake (Favaron et al., 1988; Novelli et al., 1987; Novelli<br>and Henneberry, 1987; Wrobleweski et al., 1987). The<br>action cells have shown NMDA- and kainate-dependent in-<br>creases in cGMP, with concomitant increases in Ca<sup>2+</sup><br>uptake (Favaron et al., 1988; Novelli et al., 1987; Novelli<br>and Henneberry, 1987; Wrobleweski et al., 1987). The<br>action uptake (Favaron et al., 1988; Novelli et al., 1987; Nove<br>and Henneberry, 1987; Wrobleweski et al., 1987). T<br>actions of NMDA also were antagonized by Mg<sup>2+</sup>, cor<br>petitive NMDA antagonists, and PCP agonists and w<br>modulated b and Henneberry, 1987; Wrobleweski et al., 1987). The<br>actions of NMDA also were antagonized by  $Mg^{2+}$ , com-<br>petitive NMDA antagonists, and PCP agonists and were<br>modulated by allosteric glycine receptor agonists (Wrob-<br>lew petitive NMDA antagonists, and PCP agonists and were<br>modulated by allosteric glycine receptor agonists (Wrob-<br>leweski et al., 1989). In cerebellar granule cell cultures,<br>sodium nitroprusside stimulates guanylate cyclase an modulated by allosteric glycine receptor agonists (Wrob-<br>leweski et al., 1989). In cerebellar granule cell cultures,<br>sodium nitroprusside stimulates guanylate cyclase and<br>augments cGMP levels (Novelli et al., 1987; Novelli leweski et al., 1989). In cerebellar granule cell cultures,<br>sodium nitroprusside stimulates guanylate cyclase and<br>augments cGMP levels (Novelli et al., 1987; Novelli and<br>Henneberry, 1987). NMDA-dependent c-fos expression<br>h sodium nitroprusside stimulates guanylate cyclase and<br>augments cGMP levels (Novelli et al., 1987; Novelli and<br>Henneberry, 1987). NMDA-dependent c-fos expression<br>has been shown to occur in the cascade of information<br>transfe augments cGMP levels (Novelli et al., 1987; Novelli and<br>Henneberry, 1987). NMDA-dependent c-fos expression<br>has been shown to occur in the cascade of information<br>transfer to the nucleus of these cells (Szekely et al.,<br>1989) Henneberry, 1987). NMDA-dependent c-fos expression<br>has been shown to occur in the cascade of information<br>transfer to the nucleus of these cells (Szekely et al.,<br>1989). In toto, these data are consistent with the presence<br>o has been shown to occur in the cascade of information<br>transfer to the nucleus of these cells (Szekely et al.,<br>1989). In toto, these data are consistent with the presence<br>of both NMDA and kainate EAA receptors on granule<br>ce 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 GA 1989). In toto, these data are consistent with the preserved footh NMDA and kainate EAA receptors on grancells. Cultured granule cells also possess function GABA-A receptors (Meier et al., 1984; Vaccarino et 1987) and show of both NMDA and kainate EAA receptors on granucells. Cultured granule cells also possess function GABA-A receptors (Meier et al., 1984; Vaccarino et a<br>1987) and show NMDA-dependent increases in metablism of inositol phosp **III. Intracerebellar Systems**<br>III. **Intracerebellar Systems**<br>III. **Intracerebellar Systems**<br>III. **Intracerebellar Systems**<br>III. Intracerebellar Systems 1987) and show NMDA-dependent increases in metal<br> *A. Excitatory Amino Acid and GABAergic Pathways*<br> *A. Excitatory Amino Acid and GABAergic Pathways*<br>
The cerebellum is a unique CNS area for biochemic

# III. Intracerebellar Systems<br>A. Excitatory Amino Acid and GABAergic Pathways<br>The cerebellum is a unique CNS area for biochemical

III. Intracerebellar Systems<br>A. Excitatory Amino Acid and GABAergic Pathways<br>The cerebellum is a unique CNS area for biochemi<br>studies in that a large number of the neuronal part<br>pants in the afferent, efferent, and endogen A. *Excitatory Amino Acid and GABAergic Pathways*<br>The cerebellum is a unique CNS area for biochemical<br>studies in that a large number of the neuronal partici-<br>pants in the afferent, efferent, and endogenous circuitry<br>are ch A. *Excludory Amino Acta and GABAergic Pathways*<br>The cerebellum is a unique CNS area for biochemical<br>studies in that a large number of the neuronal partici-<br>pants in the afferent, efferent, and endogenous circuitry<br>are che 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 pants in the afferent, efferent, and endogenous circuitry<br>are chemically characterized. Indeed, the only output<br>neuron of the cerebellum, the Purkinje cell (fig. 1), is<br>known to be GABAergic (Palay and Chan-Palay, 1974).<br>S are chemically characterized. Indeed, the only output<br>neuron of the cerebellum, the Purkinje cell (fig. 1), is<br>known to be GABAergic (Palay and Chan-Palay, 1974).<br>Similarly, the inhibitory interneurons (fig. 1) of the<br>mole



of the molecular (M.L.) and granular (G.L.) cell layers. DA, dopamine; ACh , acetylcholine.

**cGMP IN THE CEF**<br>**granule cell layer** (Golgi cells) are all GABAergic (Palay ea<br>**and Chan-Palay, 1974). The granule cell population of** gu cGMP IN THE CE<br>granule cell layer (Golgi cells) are all GABAergic (Palay eand Chan-Palay, 1974). The granule cell population of gr<br>the granular layer of the cerebellum utilizes an EAA as vi CGMP IN THE CEF<br>granule cell layer (Golgi cells) are all GABAergic (Palay<br>and Chan-Palay, 1974). The granule cell population of gu<br>the granular layer of the cerebellum utilizes an EAA as<br>its transmitter (Drejer et al., 198 granule cell layer (Golgi cells) are all GABAergic (Palay<br>and Chan-Palay, 1974). The granule cell population of<br>the granular layer of the cerebellum utilizes an EAA as<br>its transmitter (Drejer et al., 1983; Young et al., 19 the granular laver 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 its transmitter (Drejer et al., 1983; Young et al., 1974),<br>as do the climbing fibers that derive from neurons in the<br>inferior olive (McBride et al., 1978; Nadi et al., 1977;<br>Roffer-Tarlov and Siman, 1978). In contrast, the as do the climbing fibers that derive from neurons is<br>inferior olive (McBride et al., 1978; Nadi et al., 1<br>Roffer-Tarlov and Siman, 1978). In contrast, the ne<br>chemical makeup of mossy fiber pathways is less<br>defined and wil

delicate physiological balance between the EAA and GA-<br>BAergic pathways within the cerebellum (Lehmann and Wood, 1988; Martin and Wood, 1987; Wood et al., 1988a). chemical makeup of mossy fiber pathways is less well 199<br>defined and will be discussed later (section V.A) stra<br>Both neurochemical and anatomical data suggest a cGl<br>delicate physiological balance between the EAA and GA-<br>fr defined and will be discussed later (section V.A)<br>Both neurochemical and anatomical data suggest a<br>delicate physiological balance between the EAA and GA-<br>BAergic pathways within the cerebellum (Lehmann and<br>Wood, 1988; Mart Both neurochemical and anatomical data suggest a<br>delicate physiological balance between the EAA and GA-<br>free BA ergic pathways within the cerebellum (Lehmann and in<br>Wood, 1988; Martin and Wood, 1987; Wood et al., 1988a).<br>I delicate physiological balance between the EAA and GA<br>BAergic pathways within the cerebellum (Lehmann an<br>Wood, 1988; Martin and Wood, 1987; Wood et al., 1988a<br>Indeed, this suggestion is borne out by a large number c<br>pharma BAergic pathways within the cerebellum (Lehmann a<br>Wood, 1988; Martin and Wood, 1987; Wood et al., 1988<br>Indeed, this suggestion is borne out by a large number<br>pharmacological studies of cerebellar cGMP levels. Ho<br>ever, the Wood, 1988; Martin and Wood, 1987; Wood et al., 1988a). Condeed, this suggestion is borne out by a large number of condenancological studies of cerebellar cGMP levels. How-<br>pharmacological studies of cerebellar cGMP level Indeed, this suggestion is borne out by a large number of<br>pharmacological studies of cerebellar cGMP levels. How-<br>ever, the site of generation of cGMP within the cerebel-<br>lum has been a difficult issue to address and has r pharmacological studies of cerebellar cGMP levels. How<br>ever, the site of generation of cGMP within the cerebel<br>lum has been a difficult issue to address and has require<br>a number of experimental approaches. Initially, a dir ever, the site of generation of cGMP within the cerebel-<br>lum has been a difficult issue to address and has required (see<br>a number of experimental approaches. Initially, a direct met<br>correlation between Purkinje cell firing lum has been a difficult issue to address and has required (see a number of experimental approaches. Initially, a direct metrogreation between Purkinje cell firing rates and cere-<br>bellar cGMP levels (Biggio et al., 1977b,d a number of experimental approaches. Initially, a direct<br>correlation between Purkinje cell firing rates and cere-<br>bellar cGMP levels (Biggio et al., 1977b,d; Biggio and<br>Guidotti, 1976; Wood et al., 1982), along with the hi correlation between Purkinje cell firing rates and cere-<br>bellar cGMP levels (Biggio et al., 1977b,d; Biggio and v<br>Guidotti, 1976; Wood et al., 1982), along with the high<br>revels of guanylate cyclase in Purkinje cells (Aria bellar cGMP levels (Biggio et al., 1977b,d; Biggio and variation of the cyclic cells of guanylate cyclase in Purkinje cells (Ariano et intimal., 1982), led to the suggestion that cGMP is generated cells and that levels of Guidotti, 1976; Wood et al., 1982), along with the high<br>levels of guanylate cyclase in Purkinje cells (Ariano et ideal, 1982), led to the suggestion that cGMP is generated<br>in these cells and that levels of this cyclic nuc levels of guanylate cyclase in Purkinje cells (Ariano et intimedial, 1982), led to the suggestion that cGMP is generated cell<br>in these cells and that levels of this cyclic nucleotide are cG<br>a biochemical index of Purkinje al., 1982), led to the suggestion that cGMP is generated<br>in these cells and that levels of this cyclic nucleotide are cGl<br>a biochemical index of Purkinje cell activity (Biggio et <sup>et a</sup><br>al., 1977b,d). However, subsequent 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, al., 1977b,d). However, subsequent experiments with al., 1977b,d). However, subsequent experiments with 1990; Wood, 1990). Such a mechanism allows a large granule cell cultures demonstrated that cGMP can also be generated in these cell types (McCaslin and Morgan, small inc granule cell cultures demonstrated that cGMP can also<br>be generated in these cell types (McCaslin and Morgan,<br>1987; Novelli et al., 1987; Novelli and Henneberry, 1987).<br>Studies in which cell fractionation was used supported 1987; Novelli et al., 1987; Novelli and Henneberry, 1987).<br>Studies in which cell fractionation was used supported<br>the generation of cGMP in granule cells but not Purkinje<br>cells (Garthwaite and Garthwaite, 1987). Additional 1987; Novelli et al., 1987; Novelli and Henneberry, 1987).<br>
Studies in which cell fractionation was used supported cGM<br>
the generation of cGMP in granule cells but not Purkinje (We<br>
cells (Garthwaite and Garthwaite, 1987) Studies in which cell fractionation was used supported<br>the generation of cGMP in granule cells but not Purkinje<br>cells (Garthwaite and Garthwaite, 1987). Additionally,<br>the generation of cGMP in glial cells was suggested by the generation of cGMP in granule cells but not Purking<br>cells (Garthwaite and Garthwaite, 1987). Additionally<br>the generation of cGMP in glial cells was suggested b<br>these cell fractionation approaches (Garthwaite an<br>Garthwa cells (Garthwaite and Garthwaite, 1987). Additionally,<br>the generation of cGMP in glial cells was suggested by<br>these cell fractionation approaches (Garthwaite and<br>Garthwaite, 1987). Such data are consistent with a num-<br>ber the generation of cGMP in glial cells was suggested by<br>
these cell fractionation approaches (Garthwaite and<br>
Garthwaite, 1987). Such data are consistent with a num-<br>
ber of immunohistochemical studies (Chan-Palay and<br>
Pala these cell fractionation approaches (Garthwaite Garthwaite, 1987). Such data are consistent with a n<br>ber of immunohistochemical studies (Chan-Palay<br>Palay, 1979; Cumming et al., 1979; de Vente et al., 19<br>which have demonstr Garthwaite, 1987). Such data are consistent with a number<br>of immunohistochemical studies (Chan-Palay and class particle and Palay, 1979; Cumming et al., 1979; de Vente et al., 1989)<br>which have demonstrated basal and sodiu ber of immunohistochemical studies (Chan-Palay and Palay, 1979; Cumming et al., 1979; de Vente et al., 1989)<br>which have demonstrated basal and sodium nitroprus-<br>side-dependent increases in cGMP in the Bergmann glia<br>of the Palay, 1979; Cumming et al., 1979; de Vente et al., 1989)<br>which have demonstrated basal and sodium nitroprus-<br>side-dependent increases in cGMP in the Bergmann glia<br>of the Purkinje cell layer, in the Bergmann glial fibers o which have demonstrated basal and sodium nitroprus-<br>side-dependent increases in cGMP in the Bergmann glia<br>of the Purkinje cell layer, in the Bergmann glial fibers of<br>the molecular layer, and in the astroglia of the granul side-dependent increases in cGMP in the Bergmann glia<br>of the Purkinje cell layer, in the Bergmann glial fibers of<br>the molecular layer, and in the astroglia of the granular<br>cell layer. No cGMP was demonstrated in Purkinje c the molecular layer, and in the astroglia of the granular<br>cell layer. No cGMP was demonstrated in Purkinje cells<br>or granule cells when immunohistochemical techniques<br>were used. Under conditions of nitroprusside stimula-<br>ti the molecular layer, and in the astroglia of the granular<br>cell layer. No cGMP was demonstrated in Purkinje cells<br>or granule cells when immunohistochemical techniques<br>were used. Under conditions of nitroprusside stimula-<br>t cell layer. No cGMP was demonstrated in Purkinje cells<br>or granule cells when immunohistochemical techniques<br>were used. Under conditions of nitroprusside stimula-<br>ion, low levels of cGMP could be demonstrated in fibers<br>in t or granule cells when immunohistochemical techniques<br>were used. Under conditions of nitroprusside stimula-<br>tion, low levels of cGMP could be demonstrated in fibers<br>in the granule cell layer, which might be mossy fiber<br>inpu 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 observ tion, low levels of cGMP could be demonstrated in fibers<br>in the granule cell layer, which might be mossy fiber<br>inputs (de Vente et al., 1989). These histochemical ob-<br>servations suggest that a component of the increased<br>cG in the granule cell layer, which might be mossy fiber<br>inputs (de Vente et al., 1989). These histochemical ob-<br>servations suggest that a component of the increased<br>cGMP levels observed in cerebellar granule cell cultures<br>(s 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 agoni servations suggest that a component of the increduct control (section II.F.3), after the addition of EAA rece in this sumptify involve the  $2-10\%$  glial cell contract of such cultures (Drejer and Schousbe, 1989). Biochem MP levels observed in cerebellar granule cell culture<br>sction II.F.3), after the addition of EAA receptor a<br>sts, might involve the 2–10% glial cell contaminat<br>such cultures (Drejer and Schousbe, 1989).<br>Biochemical studies o (section II.F.3), after the addition of EAA receptor ago-<br>nists, might involve the  $2-10\%$  glial cell contamination<br>of such cultures (Drejer and Schousbe, 1989).<br>Biochemical studies of cerebellar soluble and particu-<br>lat

nists, might involve the 2–10% glial cell contamination<br>of such cultures (Drejer and Schousbe, 1989).<br>Biochemical studies of cerebellar soluble and particu-<br>late cell fractions have clearly demonstrated stimulation<br>of guan of such cultures (Drejer and Schousbe, 1989). a<br>Biochemical studies of cerebellar soluble and particu-<br>late cell fractions have clearly demonstrated stimulation<br>of guanylate cyclase by sodium nitroprusside, a drug that G<br>s

granule cell layer (Golgi cells) are all GABAergic (Palay early data suggested that NO can activate cerebellar<br>and Chan-Palay, 1974). The granule cell population of guanylate cyclase to generate increased GMP levels in<br>the Roffer-Tarlov and Siman, 1978). In contrast, the neuro-<br>
chemical makeup of mossy fiber pathways is less well<br>
1990b; Wood and Rao, 1990; Wood, 1990) have demon-<br>
defined and will be discussed later (section V.A)<br>
Both neu EREBELLUM<br>early data suggested that NO can activate cerebellar<br>guanylate cyclase to generate increased cGMP levels in EREBELLUM<br>early data suggested that NO can activate cerebellar<br>guanylate cyclase to generate increased cGMP levels in<br>vitro. In efforts to define the locus of cGMP generation 5<br>early data suggested that NO can activate cerebellar<br>guanylate cyclase to generate increased cGMP levels in<br>vitro. In efforts to define the locus of cGMP generation<br>and the possible role of NO in cGMP formation, pharearly data suggested that NO can activate cerebells<br>guanylate cyclase to generate increased cGMP levels i<br>vitro. In efforts to define the locus of cGMP generatio<br>and the possible role of NO in cGMP formation, phar-<br>macolog early data suggested that NO can activate cerebellar<br>guanylate cyclase to generate increased cGMP levels in<br>vitro. In efforts to define the locus of cGMP generation<br>and the possible role of NO in cGMP formation, phar-<br>maco guanylate cyclase to generate increased cGMP levels in<br>vitro. In efforts to define the locus of cGMP generation<br>and the possible role of NO in cGMP formation, phar-<br>macological experiments both in vitro with cerebellar<br>sli vitro. In efforts to define the locus of cGMP generation<br>and the possible role of NO in cGMP formation, phar-<br>macological experiments both in vitro with cerebellar<br>slices (Bredt and Snyder, 1989; Garthwaite et al., 1988;<br>G and the possible role of NO in cGMP formation, ph<br>macological experiments both in vitro with cerebel<br>slices (Bredt and Snyder, 1989; Garthwaite et al., 19<br>Garthwaite et al., 1989a,b) and in vivo (Wood et a<br>1990b; Wood and macological experiments both in vitro with cerebellar<br>slices (Bredt and Snyder, 1989; Garthwaite et al., 1988;<br>Garthwaite et al., 1989a,b) and in vivo (Wood et al.,<br>1990b; Wood and Rao, 1990; Wood, 1990) have demon-<br>strate slices (Bredt and Snyder, 1989; Garthwaite et al., 1988;<br>Garthwaite et al., 1989a,b) and in vivo (Wood et al.,<br>1990b; Wood and Rao, 1990; Wood, 1990) have demon-<br>strated that EAA-dependent increases in cerebellar<br>cGMP are 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 cGMP are dependent upon the prior formation of NO<br>from arginine via NO synthase. Thus, the NO synthase<br>inhibitor, N-monomethyl-L-arginine, after direct intra-<br>cerebellar administration, will antagonize increases in<br>cerebel strated that EAA-dependent increases in cerebellar<br>cGMP are dependent upon the prior formation of NO<br>from arginine via NO synthase. Thus, the NO synthase<br>inhibitor, N-monomethyl-L-arginine, after direct intra-<br>cerebellar a cGMP are dependent upon the prior formation of NO<br>from arginine via NO synthase. Thus, the NO synthase<br>inhibitor, N-monomethyl-L-arginine, after direct intra-<br>cerebellar administration, will antagonize increases in<br>cerebel from arginine via NO synthase. Thus, the NO synthase<br>inhibitor, N-monomethyl-L-arginine, after direct intra-<br>cerebellar administration, will antagonize increases in<br>cerebellar cGMP elicited by the EAA agonists (section<br>III inhibitor, N-monomethyl-L-arginine, after direct intra-<br>cerebellar administration, will antagonize increases in<br>cerebellar CGMP elicited by the EAA agonists (section<br>III.B.6) NMDA, kainate, and quisqualate as well as by<br>ph cerebellar administration, will antagonize increases increbellar cGMP elicited by the EAA agonists (section III.B.6) NMDA, kainate, and quisqualate as well as the pharmacologically induced EAA release after harmaline (sect 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) treatmen III.B.6) NMDA, kainate, and quisqualate as well as by<br>pharmacologically induced EAA release after harmaline<br>(section IV) or pentylenetetrazol (section III.B.6) treat-<br>ment (Wood et al., 1990b; Wood and Rao, 1990; Wood<br>1990 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 activatio ment (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 intercel 1990). These data have led to the hypothesis that acti-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 vation of EAA receptors on granule and Purkinje cells<br>results in the formation of NO, which is a diffusible<br>intercellular communicator entering glial and neuronal<br>cells where it activates guanylate cyclase and augments<br>cGM results in the formation of NO, which is a diffusible<br>intercellular communicator entering glial and neuronal<br>cells where it activates guanylate cyclase and augments<br>cGMP formation (Bredt and Synder, 1989; Garthwaite<br>et al. intercellular communicator entering glial and neuronal<br>cells where it activates guanylate cyclase and augments<br>cGMP formation (Bredt and Synder, 1989; Garthwaite<br>et al., 1988, 1989a,b; Wood et al., 1990b; Wood and Rao,<br>199 cells where it activates guanylate cyclase and augments<br>cGMP formation (Bredt and Synder, 1989; Garthwaite<br>et al., 1988, 1989a,b; Wood et al., 1990b; Wood and Rao,<br>1990; Wood, 1990). Such a mechanism allows a large<br>amplifi 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 i 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 a 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 gener small increase in EAA input to the neurons generating<br>NO and explains the steep dose-response curves for<br>cGMP generation noted with EAA receptor agonists<br>(Wood et al., 1989a)<br>The anatomical proximity of glial cells and the nall increase in EAA input to the neurons generatin<br>
O and explains the steep dose-response curves fo<br>
NMP generation noted with EAA receptor agonist<br>
Vood et al., 1989a)<br>
The anatomical proximity of glial cells and their

NO and explains the steep dose-response curves for<br>cGMP generation noted with EAA receptor agonists<br>(Wood et al., 1989a)<br>The anatomical proximity of glial cells and their com-<br>plex associations with neurons (Hatten et al., cGMP generation noted with EAA receptor agonists<br>
(Wood et al., 1989a)<br>
The anatomical proximity of glial cells and their com-<br>
plex associations with neurons (Hatten et al., 1984; Palay<br>
and Chan-Palay, 1974; Reese et al. (Wood et al., 1989a)<br>The anatomical proximity of glial cells and their com-<br>plex associations with neurons (Hatten et al., 1984; Palay<br>and Chan-Palay, 1974; Reese et al., 1985) also allows<br>rapid entry of NO for activation The anatomical proximity of glial cells and their com-<br>plex associations with neurons (Hatten et al., 1984; Palay<br>and Chan-Palay, 1974; Reese et al., 1985) also allows<br>rapid entry of NO for activation of glial guanylate c plex associations with neurons (riatten et al., 1984; Palay<br>and Chan-Palay, 1974; Reese et al., 1985) also allows<br>rapid entry of NO for activation of glial guanylate cy-<br>clase. Indeed, the immunohistochemistry of cGMP in<br>g rapid entry of NO for activation of gilal guanyiate cy-<br>clase. Indeed, the immunohistochemistry of cGMP in<br>glia demonstrated glial processes around Purkinje cells,<br>around synapses between Purkinje cell thorns and axonal<br>bo clase. Indeed, the Immunonistochemistry of CGMP In<br>glia demonstrated glial processes around Purkinje cells,<br>around synapses between Purkinje cell thorns and axonal<br>boutons, around mossy fiber rosettes, and around granule<br>c gna demonstrated gnal processes around rurking cens,<br>around synapses between Purkinje cell thorns and axonal<br>boutons, around mossy fiber rosettes, and around granule<br>cells (Chan-Palay and Palay, 1979). Biochemical studies<br> around synapses between Furking centrofns and axonal<br>boutons, around mossy fiber rosettes, and around granule<br>cells (Chan-Palay and Palay, 1979). Biochemical studies<br>also have demonstrated an enrichment of guanylate cy-<br>cl potently stimulated an enrichment of guanylate cy-<br>clase in freshly isolated cerebellar glial cell fractions<br>(Bunn et al., 1986). This glial enzyme was found to be<br>potently stimulated by sodium nitroprusside. However,<br>the (Bunn et al., 1986). This glial enzyme was found to be potently stimulated by sodium nitroprusside. However, the functional role of  $\text{GMP}$  as a second messenger in glial cells remains to be defined.<br>B. Pharmacology potently stimulated by sodium nitroprusside. However,

*1. y-Aminobutyric acid-A/benzodiazepine receptor modulators.* The GABA-A/benzodiazepine<br>*modulators.* The GABA-A/benzodiazepine<br>channel macroreceptor complex consists of a nu B. Pharmacology<br>
1.  $\gamma$ -Aminobutyric acid-A/benzodiazepine receptor<br>
modulators. The GABA-A/benzodiazepine/chloride<br>
channel macroreceptor complex consists of a number of<br>
protein subunits for which the regional stoichio 1.  $\gamma$ -Aminobutyric acid-A/benzodiazepine receptor<br>modulators. The GABA-A/benzodiazepine/chloride<br>channel macroreceptor complex consists of a number of<br>protein subunits for which the regional stoichiometries<br>are under in modulators. The GABA-A/benzodiazepine/chlorochannel macroreceptor complex consists of a number protein subunits for which the regional stoichiometicare under intense investigation (Meinecke et al., 194<br>However, both recept channel macroreceptor complex consists of a number of<br>protein subunits for which the regional stoichiometries<br>are under intense investigation (Meinecke et al., 1989).<br>However, both receptor autoradiographic and immuno-<br>his protein subunits for which the regional stoichiometries<br>are under intense investigation (Meinecke et al., 1989)<br>However, both receptor autoradiographic and immuno<br>histochemical studies have demonstrated cerebella<br>GABA-A/be are under intense investigation (Meinecke et al., 1989).<br>However, both receptor autoradiographic and immuno-<br>histochemical studies have demonstrated cerebellar<br>GABA-A/benzodiazepine receptor complexes in loca-<br>tions compat

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wo<br>and basket cell bodies, and granule cells (Meinecke et<br>al., 1989; Palacios et al., 1980; Richards et al., 1987).<br>Receptor-binding and biochemical studies have also dem-<sup>6</sup><br>
and basket cell bodies, and granule cells (Meinecke e<br>
al., 1989; Palacios et al., 1980; Richards et al., 1987)<br>
Receptor-binding and biochemical studies have also dem<br>
onstrated the GABA-A/benzodiazepine receptor com and basket cell bodies, and granule cells (Meinecke et dial., 1989; Palacios et al., 1980; Richards et al., 1987). co.<br>Receptor-binding and biochemical studies have also dem-<br>onstrated the GABA-A/benzodiazepine receptor co al., 1989; Palacios et al., 1980; Richards et al., 1987).<br>Receptor-binding and biochemical studies have also demonstrated the GABA-A/benzodiazepine receptor complex on cultured (section II.F.3) and freshly isolated<br>(Olsen Receptor-binding and biochemical studies have also dem-<br>onstrated the GABA-A/benzodiazepine receptor com-<br>plex on cultured (section II.F.3) and freshly isolated b<br>(Olsen and Mikoshiba, 1978) granule cells. Consistent a<br>wit onstrated 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 plex 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 bi Isen and Mikoshiba, 1978) granule cells. Consistent<br>th these studies, Weaver mice which have a granule<br>il deficit (table 1) have a 73% loss of GABA-A receptor<br>nding in the cerebellum (Olsen and Mikoshiba, 1978).<br>In additio

with these studies, Weaver mice which have a granucell deficit (table 1) have a 73% loss of GABA-A recept<br>binding in the cerebellum (Olsen and Mikoshiba, 1978<br>In addition to the GABA-A/benzodiazepine sites<br>which drugs can cell deficit (table 1) have a 73% loss of GABA-A recepto<br>binding in the cerebellum (Olsen and Mikoshiba, 1978)<br>In addition to the GABA-A/benzodiazepine sites a<br>which drugs can modulate GABAergic transmission<br>there are anci binding in the cerebellum (Olsen and Mikoshiba, 1978).<br>In addition to the GABA-A/benzodiazepine sites at<br>which drugs can modulate GABAergic transmission,<br>there are ancillary barbiturate-binding sites on this mac-<br>romolecul which drugs can modulate GABAergic transmission,<br>there are ancillary barbiturate-binding sites on this mac-<br>romolecular complex that also can lead to allosteric<br>modulation of GABA-A receptor function. In light of the<br>large there are ancillary barbiturate-binding sites on this mac-<br>romolecular complex that also can lead to allosteric La<br>modulation of GABA-A receptor function. In light of the<br>large number of inhibitory GABA<br>ergic interneurons romolecular complex that also can lead to allosteric<br>modulation of GABA-A receptor function. In light of the<br>large number of inhibitory GABAergic interneurons<br>within the cerebellum and the availability of a large<br>number of 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 GA-BAergic tran large number of inhibitory GABAergic interneurons<br>within the cerebellum and the availability of a large<br>number of pharmacological agents to manipulate GA-<br>BAergic transmission, it is not surprising that the most<br>comprehens within the cerebellum and the availability of a large<br>number of pharmacological agents to manipulate GA-<br>BAergic transmission, it is not surprising that the most<br>comprehensive reports of the pharmacology of cerebellar<br>cGMP number of pharmacological agents to manipulate GA-<br>BAergic transmission, it is not surprising that the most<br>comprehensive reports of the pharmacology of cerebellar<br>cGMP have been concerned with the GABA-A receptor<br>complex Aergic transmission, it is not surprising that the most<br>mprehensive reports of the pharmacology of cerebellar<br>iMP have been concerned with the GABA-A receptor<br>mplex (table 3).<br>It is clear from such studies that the GABA-A

comprehensive reports of the pharmacology of cerebellar<br>cGMP have been concerned with the GABA-A receptor<br>complex (table 3).<br>It is clear from such studies that the GABA-A agonist,<br>muscimol (Biggio et al., 1977a,d; Mohler e cGMP have been concerned with the GABA-A receptor botomplex (table 3). and the GABA-A agonist, and it is clear from such studies that the GABA-A agonist, comuscimol (Biggio et al., 1977a,d; Mohler et al., 1981), intraventr complex (table 3). antage and the GABA-A agonist, complex (table 3). and the GABA-A agonist, compuscime (Biggio et al., 1977a,d; Mohler et al., 1981), 2.  $\gamma$  intraventricular GABA itself (Mao et al., 1974b), a large cere It is clear from such studies that the GABA-A agor<br>muscimol (Biggio et al., 1977a,d; Mohler et al., 193<br>intraventricular GABA itself (Mao et al., 1974b), a la<br>number of benzodiazepine agonists (table 3), the GA<br>transaminas muscimol (Biggio et al., 1977a,d; Mohler et al., 1981),<br>intraventricular GABA itself (Mao et al., 1974b), a large<br>number of benzodiazepine agonists (table 3), the GABA nu<br>transaminase inhibitor, aminooxyacetic acid (Dinnen intraventricular GABA itself (Mao et al., 1974b), a large<br>number of benzodiazepine agonists (table 3), the GABA<br>transaminase inhibitor, aminooxyacetic acid (Dinnen-<br>dahl and Gumulka, 1977), and barbiturates (section<br>III.B. number of benzodiazepine agonists (table 3), the GABA numeral and Gumulka, 1977), and barbiturates (section of III.B.5) all dramatically decrease cerebellar cGMP levels. 1 The actions of diazepam have also been shown to in transaminase inhibitor, aminooxyacetic acid (Dinnen-<br>dahl and Gumulka, 1977), and barbiturates (section<br>III.B.5) all dramatically decrease cerebellar cGMP levels.<br>The actions of diazepam have also been shown to involve<br>dec dahl and Gumulka, 1977), and barbiturates (section on III.B.5) all dramatically decrease cerebellar cGMP levels. 19<br>The actions of diazepam have also been shown to involve tic<br>decreases in cGMP in both the vermis and the c III.B.5) all dramatically decrease cerebellar cGMP levels. 1983<br>The actions of diazepam have also been shown to involve tion<br>decreases in cGMP in both the vermis and the cerebellar 1983<br>hemispheres (Rubin and Ferrendelli, The actions of diazepam have also been shown to involve<br>decreases in cGMP in both the vermis and the cerebellar<br>hemispheres (Rubin and Ferrendelli, 1977). In the case<br>of the vermis, the proportion of the total decrease in<br> decreases in cGMP in both the vermis and the cerebella<br>hemispheres (Rubin and Ferrendelli, 1977). In the case<br>of the vermis, the proportion of the total decrease in<br>cGMP observed appears to be 70% in the molecular laye<br>and 1977). 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).<br>Local intracerebellar administration of either mu

cGMP observed appears to be 70% in the molecular layer direct and 30% in the granular layer (Rubin and Ferrendelli, cel<br>1977). climate intracerebellar administration of either muscials<br>mol or diazepam induced the same degr and 30% in the granular layer (Rubin and Ferrende<br>1977).<br>Local intracerebellar administration of either mus<br>mol or diazepam induced the same degree of cGM<br>decrease as observed by parenteral drug administratio<br>actions consi 1977).<br>
Local intracerebellar administration of either musci-<br>
mol or diazepam induced the same degree of cGMP<br>
decrease as observed by parenteral drug administration,<br>
actions consistent with activation of the cerebellar<br> Local intracereberial administration of either muscrimol or diazepam induced the same degree of cGMP<br>decrease as observed by parenteral drug administration,<br>actions consistent with activation of the cerebellar<br>GABA-A/benzo not or diazepain induced the same degree of COVIT<br>decrease as observed by parenteral drug administration,<br>actions consistent with activation of the cerebellar<br>GABA-A/benzodiazepine receptor complex (Biggio et al.,<br>1977d). decrease as observed by parenteral drug administration,<br>actions consistent with activation of the cerebellar<br>GABA-A/benzodiazepine receptor complex (Biggio et al.,<br>1977d). Additionally, the actions of parenteral muscimol<br>a GABA-A/benzodiazepine receptor complex (Biggio et al., 1977d). Additionally, the actions of parenteral muscimol<br>
and diazepam were not altered by 3-acetylpyridine le-<br>
sions (section IV), indicating a lack of involvement o 1977d). Additionally, the actions of parenteral muand diazepam were not altered by 3-acetylpyridisions (section IV), indicating a lack of involvem<br>the climbing fiber system in the actions of these<br>(Biggio et al., 1977d; Bi d diazepam were not altered by 3-acetylpyridine le-<br>ons (section IV), indicating a lack of involvement of<br>e climbing fiber system in the actions of these drugs<br>iggio et al., 1977d; Biggio and Guidotti, 1976).<br>The actions o

sions (section IV), indicating a lack of involvement of<br>the climbing fiber system in the actions of these drugs<br>(Biggio et al., 1977d; Biggio and Guidotti, 1976).<br>The actions of diazepam in decreasing basal cerebellar<br>cGMP the climbing fiber system in the actions of these drugs (Biggio et al., 1977d; Biggio and Guidotti, 1976).<br>The actions of diazepam in decreasing basal cerebellar<br>cGMP were potently blocked by the benzodiazepine re-<br>ceptor (Biggio et al., 1977d; Biggio and Guidotti, 1976). leverthe actions of diazepam in decreasing basal cerebellar than cGMP were potently blocked by the benzodiazepine receptor antagonist, flumazenil (Mohler et al., 1981), th The actions of diazepam in decreasing basal cerebellar tage.<br>  $cGMP$  were potently blocked by the benzodiazepine re-<br>
ceptor antagonist, flumazenil (Mohler et al., 1981), the<br>
whereas the actions of muscimol and barbiturat 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 ceptor antagonist, flumazenil (Mohler et al., 1981), thereas the actions of muscimol and barbiturates were (unaltered by this antagonist. These data support the involvement of benzodiazepine receptors in the actions word b whereas the actions of muscimol and barbiturates were<br>unaltered by this antagonist. These data support the<br>involvement of benzodiazepine receptors in the actions<br>of benzodiazepines, a suggestion previously proposed<br>based o unaltered by this antagonist. These data support the 3. Adenosine modulators. Autoradiographic studies<br>involvement of benzodiazepine receptors in the actions were the first to clearly localize  $A_1$  receptors to cerebella involvement of benzodiazepine receptors in the actions were<br>of benzodiazepines, a suggestion previously proposed grant<br>based on correlations between benzodiazepine receptor numb<br>affinity and potency to decrease cerebellar of benzodiazepines, a suggestion previously probased on correlations between benzodiazepine reaffinity and potency to decrease cerebellar cGMP (Costa et al., 1975). Additionally, the active diametabolites, desmethyldiazepa

woop<br>and basket cell bodies, and granule cells (Meinecke et diazepam, were also active in decreasing cerebellar<br>al., 1989; Palacios et al., 1980; Richards et al., 1987). cGMP levels (Govoni et al., 1976). The atypical anxi D<br>diazepam, were also active in decreasing cerebellar<br>cGMP levels (Govoni et al., 1976). The atypical anxiol-D<br>diazepam, were also active in decreasing cerebel<br>cGMP levels (Govoni et al., 1976). The atypical anxi<br>ytic agents, zopiclone, CL 218,872, and CGS 9895, whi D<br>diazepam, were also active in decreasing cerebellar<br>cGMP levels (Govoni et al., 1976). The atypical anxiol-<br>ytic agents, zopiclone, CL 218,872, and CGS 9895, which<br>also decrease cerebellar cGMP levels, were antagonized diazepam, were also active in decreasing cerebellar<br>cGMP levels (Govoni et al., 1976). The atypical anxiol-<br>ytic agents, zopiclone, CL 218,872, and CGS 9895, which<br>also decrease cerebellar cGMP levels, were antagonized<br>by diazepam, 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 fl 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 a ytic agents, zopiclone, CL<br>also decrease cerebellar of<br>by flumazenil, indicating<br>also mediate their action<br>al., 1984b, 1986).<br>Benzodiazepine invers so decrease cerebellar cGMP levels, were antagonized<br>
flumazenil, indicating that benzodiazepine receptors<br>
so mediate their actions (Mohler et al., 1981; Wood et<br>
, 1984b, 1986).<br>
Benzodiazepine inverse agonists have the

In addition to the GABA-A/benzodiazepine sites at cGMP (Wood et al., 1984c). These include methyl- $\beta$ -<br>which drugs can modulate GABAergic transmission, carboline-3-carboxylate (Burkard et al., 1985), ethyl- $\beta$ -<br>there ar by flumazenil, indicating that benzodiazepine receptors<br>also mediate their actions (Mohler et al., 1981; Wood et<br>al., 1984b, 1986).<br>Benzodiazepine inverse agonists have the opposite<br>pharmacological profile in that they inc also mediate their actions (Mohler et al., 1981; Wood., 1984b, 1986).<br>
Benzodiazepine inverse agonists have the oppo<br>
pharmacological profile in that they increase cerebe<br>
cGMP (Wood et al., 1984c). These include methy<br>
ca al., 1984b, 1986).<br>Benzodiazepine inverse agonists have the oppos<br>pharmacological profile in that they increase cerebel<br>cGMP (Wood et al., 1984c). These include methyl<br>carboline-3-carboxylate (Burkard et al., 1985), ethyl<br> Benzodiazepine inverse agonists have the opposite<br>pharmacological profile in that they increase cerebellar<br>cGMP (Wood et al., 1984c). These include methyl- $\beta$ -<br>carboline-3-carboxylate (Burkard et al., 1985), ethyl- $\beta$ -<br> pharmacological profile in that they incread CGMP (Wood et al., 1984c). These includes carboline-3-carboxylate (Burkard et al., 1983), and methyl-6,7-dimethoxy-4-boline-3-carboxylate (Govoni et al. 1976). cGMP (Wood et al., 1984c). These include methyl- $\beta$ -carboline-3-carboxylate (Burkard et al., 1985), ethyl- $\beta$ -carboline-3-carboxylate (Fujimoto et al., 1982; Koe and Lebel, 1983), and methyl-6,7-dimethoxy-4-ethyl- $\beta$ -c carboline-3-carboxylate (Burkard et al., 1985), ethy<br>carboline-3-carboxylate (Fujimoto et al., 1982; Koe<br>Lebel, 1983), and methyl-6,7-dimethoxy-4-ethyl- $\beta$ -<br>boline-3-carboxylate (Govoni et al. 1976). The incre<br>in cerebell carboline-3-carboxylate (Fujimoto et al., 1982; Koe and Lebel, 1983), and methyl-6,7-dimethoxy-4-ethyl- $\beta$ -carboline-3-carboxylate (Govoni et al. 1976). The increases in cerebellar cGMP induced by these inverse benzodiaz Lebel, 1983), and methyl-6,7-dimethoxy-4-ethyl- $\beta$ -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 boline-3-carboxylate (Govoni et al. 1976). The increases<br>in cerebellar cGMP induced by these inverse benzodiaze-<br>pine agonists are reversed in a dose-dependent fashion<br>by flumazenil, indicating that their actions are medi in cerebellar cGMP induced by these inverse ber<br>pine agonists are reversed in a dose-dependent<br>by flumazenil, indicating that their actions are :<br>by benzodiazepine receptors. At doses which do<br>basal cerebellar cGMP levels pine agonists are reversed in a dose-dependent fashion<br>by flumazenil, indicating that their actions are mediated<br>by benzodiazepine receptors. At doses which do not alter<br>basal cerebellar cGMP levels, ethyl- $\beta$ -carboline-3 by flumazenil, indicating that their actions are mediated<br>by benzodiazepine receptors. At doses which do not alter<br>basal cerebellar CGMP levels, ethyl- $\beta$ -carboline-3-car-<br>boxylate (Fujimoto et al., 1982; Koe and Lebel, 1 by benzodiazep<br>basal cerebella<br>boxylate (Fujii<br>antagonizes the<br>CGMP levels.<br>2.  $\gamma$ -Aminobi *2. 2. 2. y-Aminobushine accompacies the depressant actions of diazepam on 2. y-Aminobutyric acid-B receptor agonists.* Within the rebellum, GABA-B receptors have been observed at a

in cerebellar CGMP induced by these inverse benzodiaze-<br>pine agonists are reversed in a dose-dependent fashion<br>by flumazenil, indicating that their actions are mediated<br>by benzodiazepine receptors. At doses which do not a antagonizes the depressant actions of diazepam on  $cGMP$  levels.<br>  $2. \gamma$ -Aminobutyric acid-B receptor agonists. Within the cerebellum, GABA-B receptors have been observed at a number of anatomical loci that can effectively cGMP levels.<br>
2.  $\gamma$ -Aminobutyric acid-B receptor agonists. Within the cerebellum, GABA-B receptors have been observed at number of anatomical loci that can effectively modulat cGMP levels. Lesions with 3-acetylpyridine 2.  $\gamma$ -*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 demo exerciencial, GABA-B receptors have been observed at a<br>number of anatomical loci that can effectively modulate<br>cGMP levels. Lesions with 3-acetylpyridine have demonstrated<br>onstrated receptors on climbing fibers (Kato and F cGMP levels. Lesions with 3-acetylpyridine have deronstrated receptors on climbing fibers (Kato and Fukud 1985), studies of mutant mice have demonstrated functionally coupled receptors on granule cells (Wojcik et a 1985), tors on entity and granule cells (Waiver and Fusure, 1985), studies of mutant mice have demonstrated functionally coupled receptors on granule cells (Wojcik et al., 1981). Therefore, these inhibitory receptors can directly tionally 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 recept 1980), and autorating rapinc 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 gra tors 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 pos et al., 1981). Therefore, these immoltory receptors can<br>directly decrease activity of both Purkinje and granule<br>cells within the cerebellum as well as decrease positive<br>climbing fiber input. Recent autoradiographic studies directly decrease activity of both Purkinje and granule<br>cells within the cerebellum as well as decrease positive<br>climbing fiber input. Recent autoradiographic studies<br>also have demonstrated a clear topographic GABA-B<br>recep cells within the cerebellum as well as decrease positivelimbing fiber input. Recent autoradiographic studies also have demonstrated a clear topographic GABA-leceptor distribution with parasaggital zones of high an low bind climbing fiber input. Recent autoradiographic studies<br>also have demonstrated a clear topographic GABA-B<br>receptor distribution with parasaggital zones of high and<br>low binding; this distribution correlates with the para-<br>sag also have demonstrated a<br>receptor distribution with plow binding; this distribution<br>saggital zonation of both aff<br>(Albin and Gilman, 1989).<br>As would be predicted by ceptor distribution with parasaggital zones of high and we binding; this distribution correlates with the paraggital zonation of both afferent and efferent pathwa lbin and Gilman, 1989).<br>As would be predicted by the GABA-B

**bution, backofferent and efferent pathways**<br> **(Albin and Gilman, 1989).**<br> **As would be predicted by the GABA-B receptor distri-**<br>
bution, baclofen, an agonist at these receptors, dose<br>
dependently (Gumulka et al., 1979a) (Albin and Gilman, 1989).<br>As would be predicted by the GABA-B receptor distribution, baclofen, an agonist at these receptors, dose<br>dependently (Gumulka et al., 1979a) and time depend-<br>ently (Mailman et al., 1978) decrease 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. Pre bution, baclofen, an agonist at these receptors, dose<br>dependently (Gumulka et al., 1979a) and time depend-<br>ently (Mailman et al., 1978) decreased cerebellar cGMP<br>levels. Pretreatment with baclofen also was able to an-<br>tago dependently (Gumulka et al., 1979a) and time dependently (Mailman et al., 1978) decreased cerebellar cGMP<br>levels. Pretreatment with baclofen also was able to antagonize the increases in cerebellar cGMP evoked by the<br>GABAer ently (Mailman et al., 1978) decreased cerebellar cGMP<br>levels. Pretreatment with baclofen also was able to an-<br>tagonize the increases in cerebellar cGMP evoked by the<br>GABAergic antagonists, isoniazid and picrotoxin, but no levels. Pretreatment with<br>tagonize the increases in GABAergic antagonists, is<br>those evoked by either<br>(Gumulka et al., 1979a).<br>3. Adenosine modulat gonize the increases in cerebellar cGMP evoked by the<br>ABAergic antagonists, isoniazid and picrotoxin, but not<br>ose evoked by either pentylenetetrazol or arecoline<br>lumulka et al., 1979a).<br>3. Adenosine modulators. Autoradiogr

The first to clearly localize A<sub>1</sub> receptors to cerebellar<br>  $\alpha$  *Adenosine modulators.* Autoradiographic studies<br>
were the first to clearly localize A<sub>1</sub> receptors to cerebellar<br>
granule cells and to demonstrate a decrea Granulka et al., 1979a).<br>
3. *Adenosine modulators*. Autoradiographic studies<br>
were the first to clearly localize A<sub>1</sub> receptors to cerebellar<br>
granule cells and to demonstrate a decrease in their<br>
numbers in Weaver but no 3. Adenosine modulators. Autoradiographic studies<br>were the first to clearly localize  $A_1$  receptors to cerebellar<br>granule cells and to demonstrate a decrease in their<br>numbers in Weaver but not Nervous mice (table 1;<br>Good granule cells and to demonstrate a decrease in their Goodman and Snyder, 1982; Goodman et al., 1983).

# **CGMP IN THE CEREBELLUM** 7

THE CEREBELLU<br>TABLE 3<br>P in the cerebellum **CGMP IN THE CEREBELLUM**<br>TABLE 3<br>*Drug effects on cerebellar cGMP in the cerebellum of the rat and mouse*\*





# TABLE 3-Continued



PHARM<br>REV



# **cGMP IN THE CEREBELLUM** 9 CGMP IN THE CEREBELLUM<br>TABLE 3-Continued



## 10 WOOD

# WOOD<br>TABLE 3-Continued









NECA<br>
10 mg<br>
25 mg ip 120 min 70 M Wood et al., 1999b<br>
25 mg ip 135 min 100 M Wood et al., 1989b<br>
25 mg ip 135 min 100 M Wood et al., 1989b<br>
26 mg ip 135 min 100 M Wood et al., 1989b<br>
26 mg ip 135 min 100 M Wood et al., 19 \* Abbreviations: AP5, aminophosphonopentanoate; AP7, aminophosphonohetanoate; CCE, ethyl  $\beta$ -carboline-3-carboxylate; CCM, methyl  $\beta$ -carboline-3-carboxylate; DMCM, methyl 6,7-dimethyoxy-4-ethyl- $\beta$ -carboline-3-carboxy carboline-3-carboxylate; DMCM, methyl 6,7-dimethyoxy-4-ethyl- $\beta$ -carboline-3-carboxylate; DN 141<br>proline amide; DPH, diphenylhydantoin; icb, intracerebellar; ict, intracisternal; ivt, intraventricular;<br>thiazolidine-4-carb

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PHARMACOLOGICAL REVIEWS

**a**spet

w<br>cultures supported these autoradiographic studies. Fur-<br>thermore, in vivo pharmacological studies with the aden-12<br>cultures supported these autoradiographic studies. Fu<br>thermore, in vivo pharmacological studies with the ader<br>osine agonists, cyclohexyladenosine, N-ethylcarboxam 12<br>cultures supported these autoradiographic studie<br>thermore, in vivo pharmacological studies with th<br>osine agonists, cyclohexyladenosine, N-ethylcarb<br>doadenosine, and R-phenylisopropyladenosine, a cultures supported these autoradiographic studies. Fur-<br>thermore, in vivo pharmacological studies with the aden-<br>osine agonists, cyclohexyladenosine, N-ethylcarboxami-<br>doadenosine, and R-phenylisopropyladenosine, and the<br>s cultures supported these autoradiographic st<br>thermore, in vivo pharmacological studies wit<br>osine agonists, cyclohexyladenosine, N-ethyl<br>doadenosine, and R-phenylisopropyladenosin<br>selective A<sub>1</sub> antagonist, 8-cyclopentyl-1, thermore, in vivo pharmacological studies with the adenosine agonists, cyclohexyladenosine, N-ethylcarboxami-<br>doadenosine, and R-phenylisopropyladenosine, and the<br>selective  $A_1$  antagonist, 8-cyclopentyl-1,3-dipropylxanosine agonists, cyclohexyladenosine, N-ethylcarboxami-<br>doadenosine, and R-phenylisopropyladenosine, and the<br>selective A<sub>1</sub> antagonist, 8-cyclopentyl-1,3-dipropylxan-<br>thine, demonstrated that adenosine-dependent decreases<br>i selective  $A_1$  antagonist, 8-cyclopentyl-1,3-dipropylxanthine, demonstrated that adenosine-dependent decreases<br>in cerebellar cGMP were  $A_1$  receptor mediated (Wood et al., 1989b).<br>Although these decreases in cerebellar lective  $A_1$  antagonist, 8-cyclopentyl-1,3-dipropylxan-<br>ine, demonstrated that adenosine-dependent decreases<br>cerebellar cGMP were  $A_1$  receptor mediated (Wood et<br>c. 1989b).<br>Although these decreases in cerebellar cGMP we

thine, demonstrated that adenosine-dependent decreases time<br>in cerebellar cGMP were  $A_1$  receptor mediated (Wood et cGM<br>al., 1989b).<br>Although these decreases in cerebellar cGMP were leve<br>probably mainly evoked via  $A_1$  in cerebellar cGMP were  $A_1$  receptor mediated (Wood et cal., 1989b).<br>
Although these decreases in cerebellar cGMP were leprobably mainly evoked via  $A_1$  receptors present on faranule cells, the parallel inhibitory effe al., 1989b).<br>
Although these decreases in cerebellar cGMP were<br>
probably mainly evoked via  $A_1$  receptors present on<br>
granule cells, the parallel inhibitory effects of these drugs<br>
on nigrostriatal dopamine release (Wood Although these decreases in cerebellar cGMP were lever probably mainly evoked via  $A_1$  receptors present on fectranule cells, the parallel inhibitory effects of these drugs dison nigrostriatal dopamine release (Wood et a probably mainly evoked via  $A_1$  receptors present on fects of phenobarbital were not reversed by the benzo-<br>granule cells, the parallel inhibitory effects of these drugs diazepine receptor antagonist, flumazenil (Mohler V.B.1). Improstriatal dopamine release (Wood et al., 1989b<br>Bo may have contributed to some of the net effect, vicreased mossy fiber input to the cerebellum (section B.1).<br>4. *Ethanol*. Ethanol has been shown to decrease base<br>Inter

also may have contributed to some of the net effect, via<br>decreased mossy fiber input to the cerebellum (section<br>V.B.1).<br>4. *Ethanol*. Ethanol has been shown to decrease base-<br>line levels of cerebellar cGMP (Dodson and John decreased mossy fiber input to the cerebellum (section by.B.1).<br>
4. Ethanol. Ethanol has been shown to decrease base-<br>
line levels of cerebellar cGMP (Dodson and Johnson, 1979; Ferko et al., 1982; Mailman et al., 1979; Moh V.B.1).<br>4. *Ethanol*. Ethanol has been shown to decrease ba<br>line levels of cerebellar cGMP (Dodson and Johns<br>1979; Ferko et al., 1982; Mailman et al., 1979; Mohler<br>al., 1981; Volicer and Hurter, 1977; Volicer and Kloso<br>icz 4. Ethanol. Ethanol has been shown to decrease base-<br>
line levels of cerebellar CGMP (Dodson and Johnson, Ca<br>
1979; Ferko et al., 1982; Mailman et al., 1979; Mohler et<br>
the al., 1981; Volicer and Hurter, 1977; Volicer and line 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 1979; Ferko et al., 1982; Mailman et al., 1979; Mohler et the al., 1981; Volicer and Hurter, 1977; Volicer and Klosow-sicz, 1979) with no tolerance being observed after 1 week ported after 12 days of Number to the asses be al., 1981; Volicer and Hurter, 1977; Volicer and Klosow-<br>icz, 1979) with no tolerance being observed after 1 week<br>of chronic treatment (Dodson and Johnson, 1980), al-<br>though tolerance has been reported after 12 days of<br>tre icz, 1979) with no tolerance being observed after 1 week pat<br>of chronic treatment (Dodson and Johnson, 1980), al-<br>though tolerance has been reported after 12 days of Na<br>treatment (Breese et al., 1979b). However, during alc though tolerance has been reported after 12 days of Nahrwold et al., 1977) and ether (Lust et al., 1976), also<br>treatment (Breese et al., 1979b). However, during alcohol dose dependently decreased basal cGMP levels. Simi-<br>w 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., treatment (Breese et<br>withdrawal, signific<br>(Ferko et al., 1982)<br>depressant actions<br>1979b) were noted.<br>A role for the mo thdrawal, significant increases in cerebellar cGMP larly<br>erko et al., 1982) and an increased sensitivity to the afte<br>pressant actions of alcohol on cGMP (Breese et al., 6.<br>79b) were noted. ATO<br>A role for the motor-depressa

(Ferko et al., 1982) and an increased sensitivity to the<br>depressant actions of alcohol on cGMP (Breese et al.,<br>1979b) were noted.<br>A role for the motor-depressant actions of alcohol in<br>the ethanol-dependent decreases in cGM depressant actions of alcohol on cGMP (Breese et al., 1979b) were noted. A<br>A role for the motor-depressant actions of alcohol in the ethanol-dependent decreases in cGMP has been sug-<br>gested (Breese et al., 1979b); however, 1979b) were noted.<br>
A role for the motor-depressant actions of alcohol in<br>
the ethanol-dependent decreases in CGMP has been sug-<br>
gested (Breese et al., 1979b); however, in rats paralyzed<br>
with *d*-tubocurarine and mechani A role for the motor-depressant actions of alcohol<br>the ethanol-dependent decreases in cGMP has been s<br>gested (Breese et al., 1979b); however, in rats paraly<br>with *d*-tubocurarine and mechanically ventilated, alco<br>still sig lum. with d-tubocurarine and mechanically ventilated, alcohol<br>still significantly depressed cGMP levels in the cerebel-<br>lum.<br>In addition to decreasing basal cerebellar cGMP,

still significantly depressed cGMP levels in the cerebel-<br>lum.<br>In addition to decreasing basal cerebellar cGMP,<br>ethanol also antagonizes harmaline-dependent increases<br>in cGMP (Rappaport et al., 1984), suggesting an antagstill significantly depressed cGMP levels in the cereb-<br>lum.<br>In addition to decreasing basal cerebellar cGM<br>ethanol also antagonizes harmaline-dependent increas-<br>in cGMP (Rappaport et al., 1984), suggesting an anta-<br>onism lem. 1988<br>In addition to decreasing basal cerebellar cGMP, man<br>ethanol also antagonizes harmaline-dependent increases studi<br>in cGMP (Rappaport et al., 1984), suggesting an antag-<br>onism of EAA-mediated transmission in the c In addition to decreasing basal cerebellar cGMP, methanol also antagonizes harmaline-dependent increases stincGMP (Rappaport et al., 1984), suggesting an antagonism of EAA-mediated transmission in the cerebellum respection ethanol also antagonizes harmaline-dependent increases<br>in cGMP (Rappaport et al., 1984), suggesting an antag-<br>onism of EAA-mediated transmission in the cerebellum<br>(section III.B.6). Furthermore, the mechanism of action<br>of in cGMP (Rappaport et al., 1984), suggesting an antag-<br>onism of EAA-mediated transmission in the cerebellum<br>(section III.B.6). Furthermore, the mechanism of action (I<br>of ethanol, as assessed in granule cell cultures, appea onism of EAA-mediated transmission in the cerebellum<br>(section III.B.6). Furthermore, the mechanism of action<br>of ethanol, as assessed in granule cell cultures, appears<br>to involve antagonism of NMDA-mediated activation of<br>gu (section III.B.6). Furthermore, the mechanism of action<br>of ethanol, as assessed in granule cell cultures, appears<br>to involve antagonism of NMDA-mediated activation of<br>guanylate cyclase (Hoffman et al., 1989a,b). In support of ethanol, as assessed in granule cell cultures, appears<br>to involve antagonism of NMDA-mediated activation of<br>guanylate cyclase (Hoffman et al., 1989a,b). In support<br>of this mechanism of action, the benzodiazepine recepto to involve antagonism of NMDA-mediated activation of negranylate cyclase (Hoffman et al., 1989a,b). In support mof this mechanism of action, the benzodiazepine receptor 1) antagonist, flumazenil, did not alter the depressa guanylate cyclase (Hoffman et al., 1989a,b). In suppose of this mechanism of action, the benzodiazepine recept antagonist, flumazenil, did not alter the depressant effects of ethanol on cerebellar cGMP, indicating a lack G of this mechanism<br>antagonist, fluma<br>fects of ethanol of<br>GABAergic involuer et al., 1981).<br>Chronic lithiur tagonist, flumazenil, did not alter the depressant ef-<br>ts of ethanol on cerebellar cGMP, indicating a lack of<br>prese.<br>ABAergic involvement in the actions of ethanol (Moh-<br>in the actions of ethanol (Moh-<br>in the actions of th

fects of ethanol on cerebellar cGMP, indicating a lack of pre<br>
GABAergic involvement in the actions of ethanol (Mohnicle et al., 1981).<br>
ler et al., 1981).<br>
Chronic lithium treatment (2 mEq of LiCl/kg for 10 ule<br>
days) has GABAergic involvement in the actions of ethanol (Mohler et al., 1981).<br>
Chronic lithium treatment (2 mEq of LiCl/kg for 10<br>
days) has been shown to block the decreases in cGMP<br>
induced by 3 g/kg of ethanol (Hunt and Goldma ler et al., 1981).<br>
Chronic lithium treatment (2 mEq of LiCl/kg for 10 uldays) has been shown to block the decreases in cGMP trinduced by  $3 g/kg$  of ethanol (Hunt and Goldman, 1979); Nowever, under these conditions the bloo Chronic lithium treatment  $(2 \text{ mEq of LiCl/kg}$  for 10 undays) has been shown to block the decreases in cGMP timeduced by  $3 g/kg$  of ethanol (Hunt and Goldman, 1979); Nunder these conditions the blood levels of nethanol were reduc lithium. duced by 3 g/kg of ethanol (Hunt and Goldman, 1979);<br> *wever*, under these conditions the blood levels of no<br>
hanol were reduced to 35% of those in rats not receiving<br>
hium.<br>
5. *Barbiturates and anesthetics*. Pentobarbita

however, under these conditions the blood levels of<br>ethanol were reduced to 35% of those in rats not receiving<br>lithium.<br>5. Barbiturates and anesthetics. Pentobarbital (Dodson<br>and Johnson, 1980; Kant et al., 1980; Katz and ethanol were reduced to 35% of those in rats not receiving<br>lithium.<br>5. Barbiturates and anesthetics. Pentobarbital (Dodson<br>and Johnson, 1980; Kant et al., 1980; Katz and Catravas,<br>1976; Mailman et al., 1979; Morgan and Pfe al., 5. Barbiturates and anesthetics. Pentobarbital (Dodson Hand Johnson, 1980; Kant et al., 1980; Katz and Catravas, loc.<br>1976; Mailman et al., 1979; Morgan and Pfeil, 1984; int.<br>Opmeer et al., 1976), phenobarbital (Ferre

WOOD<br>r- Kinscherf, 1977; Mailman et al., 1979; Morgan and Pfeil,<br>n- 1984). and barbital (Lane and Morgan. 1984) dose and D<br>Kinscherf, 1977; Mailman et al., 1979; Morgan and Pfeil,<br>1984), and barbital (Lane and Morgan, 1984) dose and<br>time dependently (Morgan and Pfeil, 1984) decrease D<br>Kinscherf, 1977; Mailman et al., 1979; Morgan and Pfeil,<br>1984), and barbital (Lane and Morgan, 1984) dose and<br>time dependently (Morgan and Pfeil, 1984) decrease<br>basal cerebellar cGMP and tolerance develops to these 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 1984), and barbital (Lane and Morgan, 1984) dose and<br>time dependently (Morgan and Pfeil, 1984) decrease<br>basal cerebellar cGMP and tolerance develops to these<br>actions. Interestingly, there is a dissociation between the<br>time time dependently (Morgan and Pfeil, 1984) decrease<br>basal cerebellar cGMP and tolerance develops to these<br>actions. Interestingly, there is a dissociation between the<br>time course of recovery to the motor-depressant and<br>cGMP basal cerebellar cGMP and tolerance develops to these<br>actions. Interestingly, there is a dissociation between the<br>time course of recovery to the motor-depressant and<br>cGMP effects of pentobarbital, indicating a lack of coractions. 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 lev 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 eflevels (section II.E.1; Morgan and Pfeil, 1984). The effects of phenobarbital were not reversed by the benzo-<br>diazepine receptor antagonist, flumazenil (Mohler et al., 1981), indicating a lack of involvement of benzodiazep fects of phenobarbital were not reversed by the benzo-<br>diazepine receptor antagonist, flumazenil (Mohler et al.,<br>1981), indicating a lack of involvement of benzodiazepine<br>receptors in the actions of this drug. Also of inte diazepine 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) 1981), indicating a lack of involvement of benzodiazepine<br>receptors in the actions of this drug. Also of interest<br>barbital withdrawal from dependent rats (8 weeks) has<br>been shown to result in a selective supersensitivity t receptors in the actions of this drug. Also of interest,<br>barbital withdrawal from dependent rats (8 weeks) has<br>been shown to result in a selective supersensitivity to<br>kainate-dependent increases in cerebellar cGMP (Mc-<br>Cas barbital withdrawal from dependent rats (8 weeks) has<br>been shown to result in a selective supersensitivity to<br>kainate-dependent increases in cerebellar cGMP (Mc-<br>Caslin and Morgan 1989); there was no augmentation of<br>the NM such a possible role for barbiturate modulation of<br>the NMDA or quisqualate response (III.B.6). These data<br>suggest a possible role for barbiturate modulation of EAA<br>pathways in vivo. Caslin and Morgan 1989); there was no augmentation of<br>the NMDA or quisqualate response (III.B.6). These data<br>suggest a possible role for barbiturate modulation of EAA<br>pathways in vivo. uslin and Morgan 1989); there was no augmentation of<br>e NMDA or quisqualate response (III.B.6). These data<br>ggest a possible role for barbiturate modulation of EAA<br>thways in vivo.<br>The general anesthetics, halothane (Kant et

the NMDA or quisqualate response (III.B.6). These data<br>suggest a possible role for barbiturate modulation of EAA<br>pathways in vivo.<br>The general anesthetics, halothane (Kant et al., 1980;<br>Nahrwold et al., 1977) and ether (Lu suggest a possible role for barbiturate modulation of EA<br>pathways in vivo.<br>The general anesthetics, halothane (Kant et al., 198<br>Nahrwold et al., 1977) and ether (Lust et al., 1976), als<br>dose dependently decreased basal cGM pathways in vivo.<br>
The general anesthetics, halothane (Kant et al., 1980;<br>
Nahrwold et al., 1977) and ether (Lust et al., 1976), also<br>
dose dependently decreased basal cGMP levels. Simi-<br>
larly, the local anesthetic, lidoc Nahrwold et al., 1977) and ether (Lust et al., 1976), also larly, the local anesthetic, lidocaine, decreased cGMP

dose dependently decreased basal cGMP levels. Simi-<br>larly, the local anesthetic, lidocaine, decreased cGMP<br>after parenteral administration (table 2).<br>6. Excitatory amino acid receptor modulators. a. EXCIT-<br>ATORY AMINO ACID larly, the local anesthetic, lidocaine, decreased cGMP<br>after parenteral administration (table 2).<br>6. Excitatory amino acid receptor modulators. a. EXCIT-<br>ATORY AMINO ACID AGONISTS. Within the CNS there are<br>three major EAA after parenteral administration (table 2).<br>6. Excitatory amino acid receptor modulators. a. EXCIT-<br>ATORY AMINO ACID AGONISTS. Within the CNS there are<br>three major EAA receptor subtypes as characterized by<br>their selective a 6. Excitatory amino acid receptor modulators. a. EXCIT<br>ATORY AMINO ACID AGONISTS. Within the CNS there are three major EAA receptor subtypes as characterized b<br>their selective agonists: kainate, quiqualate, and NMDA<br>Additi ATORY AMINO ACID AGONISTS. Within the CNS there are<br>three major EAA receptor subtypes as characterized by<br>their selective agonists: kainate, quiqualate, and NMDA.<br>Additionally, the NMDA receptor is a macromolecular<br>complex three major EAA receptor subtypes as characterized by<br>their selective agonists: kainate, quiqualate, and NMDA.<br>Additionally, the NMDA receptor is a macromolecular<br>complex that also contains a positive allosteric glycine<br>si their selective agonists: kainate, quiqualate, and NMDA<br>Additionally, the NMDA receptor is a macromolecula<br>complex that also contains a positive allosteric glycin<br>site and a negative allosteric PCP site (Bertlino et al<br>198 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 (Cotcomplex that also contains a positive allosteric glycine<br>site and a negative allosteric PCP site (Bertlino et al.,<br>1988; Wood et al., 1989c). Within the cerebellum (Cot-<br>man et al., 1987; Olson et al., 1987), autoradiograp 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 recep studies have demonstrated dense populations of quis-<br>qualate receptors on Purkinje cell dendrites and kainate<br>receptors on granule cells. Electrophysiological studies<br>(DuPont et al., 1984) have demonstrated that these denqualate receptors on Purkinje cell dendrites and kainate dritic quisqualate receptors are functionally coupled to<br>neuronal activity changes. In brain slices from Nervous<br>mice, possessing reduced Purkinje cell populations (table receptors on granule cells. Electrophysiological studies<br>(DuPont et al., 1984) have demonstrated that these den-<br>dritic quisqualate receptors are functionally coupled to<br>neuronal activity changes. In brain slices from Nerv (DuPont et al., 1984) have demonstrated that these dendritic quisqualate receptors are functionally coupled to<br>neuronal activity changes. In brain slices from Nervous<br>mice, possessing reduced Purkinje cell populations (tab dritic quisqualate receptors are functionally coupled to<br>neuronal activity changes. In brain slices from Nervous<br>mice, possessing reduced Purkinje cell populations (table<br>1), kainate still stimulates cGMP formation (Schmid neuronal activity changes. In brain slices from Nervous<br>mice, possessing reduced Purkinje cell populations (table<br>1), kainate still stimulates cGMP formation (Schmidt<br>and Nadi, 1977); this finding is consistent with the<br>pr 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 numb 1), kainate still stimulates cGMP formation (Schmid 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 gra and Nadi, 1977); this finding is consistent with the presence of kainate receptors on granule cells. Smal numbers of NMDA receptors also were shown to be resident on granule cells, consistent with data from gran ule cell c 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 ule cell cultures (section II.F.3). Biochemical and electrophysiological studies also support the presence of NMDA receptors on the terminals of afferent noradre-<br>nergic nerve endings in the cerebellum (Marwaha et al., 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 noradrenerg ule cell cultures (section II.F.3). Biochemical and electrophysiological studies also support the presence of NMDA receptors on the terminals of afferent noradre-<br>nergic nerve endings in the cerebellum (Marwaha et al., 198 trophysiolo<br>NMDA rec<br>nergic nerv<br>1980, 1981;<br>al., 1988).<br>Presumal 1980, 1981; Rao et al., 1990h; Wood and Rao, 1990; Yi et al., 1988).<br>Presumably, as a result of these strategic receptor

nergic nerve endings in the cerebellum (Marwaha et al., 1980, 1981; Rao et al., 1990h; Wood and Rao, 1990; Yi et al., 1988).<br>
Presumably, as a result of these strategic receptor<br>
localizations, NMDA, quisqualate, and kaina 1980, 1981; Rao et al., 1990h; Wood and Rao, 1990; Y<br>al., 1988).<br>Presumably, as a result of these strategic recep<br>localizations, NMDA, quisqualate, and kainate, a<br>intraventricular (McCaslin and Morgan, 1989), intra<br>ternal al., 1988).<br> **Presumably, as a result of these strategic recepto**<br>
localizations, NMDA, quisqualate, and kainate, afte<br>
intraventricular (McCaslin and Morgan, 1989), intracis<br>
ternal (Wood et al., 1982), and direct intrace

cGMP IN THE CEREBELLUM<br>(Wood et al., 1987, 1989a,d; Wood and Rao 1989; Wrob-<br>leweski et al., 1987) injections, increase cerebellar cGMP further defin CGMP IN THE CER<br>(Wood et al., 1987, 1989a,d; Wood and Rao 1989; Wrobleweski et al., 1987) injections, increase cerebellar cGMP<br>in a dose-dependent manner (fig. 2). Analyses of the having **in a** dose-dependent manner (fig. 2). Analyses of the interactions of NMDA with its receptor also suggest that bien interactions of NMDA with its receptor also suggest that bien **interactive CI** interactions of NMDA with its receptor also suggest that two to three molecules of NMDA with its receptor also suggest that two to three molecules of NMDA are required for actions. (Wood et al., 1987, 1989a,d; Wood and Rao 1989; Wrobleweski et al., 1987) injections, increase cerebellar cGMF in a dose-dependent manner (fig. 2). Analyses of the interactions of NMDA with its receptor also suggest that t leweski et al., 1987) injections, increase cerebellar cGMP<br>in a dose-dependent manner (fig. 2). Analyses of the<br>interactions of NMDA with its receptor also suggest that<br>two to three molecules of NMDA are required for actiinteractions of NMDA with its receptor also suggest that bitwo to three molecules of NMDA are required for activation of each NMDA receptor unit (Wood et al., 1989a), C an observation previously reported for the interactio **(Brookes** and Werman, 1973). tion of each NMDA receptor unit (Wood et al., 1989<br> **Interferent of the interaction**<br>
ABA with the GABA/benzodiazepine receptor comp<br>
rookes and Werman, 1973).<br>
Interestingly, during barbital withdrawal from depent<br>
rats,

**ent rats, there is a selective sensitization of cerebellar** qualate (McCaslin and Morgan, 1989), suggesting an (Brookes and Werman, 1973). C. (Interestingly, during barbital withdrawal from depend-<br>ent rats, there is a selective sensitization of cerebellar bell<br>cGMP responses to kainate but not to NMDA or quis-<br>qualate (McCaslin an Interestingly, during barbital withdrawal from depend-<br>ent rats, there is a selective sensitization of cerebellar bell:<br>cGMP responses to kainate but not to NMDA or quis-<br>qualate (McCaslin and Morgan, 1989), suggesting an ent rats, there is a selective sensitization of cerebellar belcGMP responses to kainate but not to NMDA or quisqualate (McCaslin and Morgan, 1989), suggesting an patindependent kainate receptor action. The increases in cli cGMP responses to kainate but not to NMDA or quis-<br>qualate (McCaslin and Morgan, 1989), suggesting an<br>independent kainate receptor action. The increases in<br>cerebellar cGMP induced by intracerebellar kainate peak<br>at 30 min qualate (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). independent kainate receptor action. The increases cerebellar cGMP induced by intracerebellar kainate pear at 30 min and are maintained for 5 h (Biggio et a 1978d). However, by 24 h, when cell death has occurre cGMP level cerebellar cGMP induced by intracerebellar kainate peak<br>at 30 min and are maintained for 5 h (Biggio et al.,<br>1978d). However, by 24 h, when cell death has occurred,<br>cGMP levels decrease to 20% of control and are main-<br>tain 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., 197 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 harmal cGMP levels decrease to 20%<br>tained at this low level for a<br>1978d). Additionally, these k<br>maline- and isoniazid-depend<br>cGMP (Biggio et al., 1978d).<br>b. N-METHYL-D-ASPARTATE 1978d). Additionally, these kainate lesions block harmaline- and isoniazid-dependent increases in cerebellar cGMP (Biggio et al., 1978d).<br> **b. N-METHYL-D-ASPARTATE-ASSOCIATED GLYCINE AG-**

maline- and isoniazid-dependent increases in cerebellar<br>cGMP (Biggio et al., 1978d).<br>b. N-METHYL-D-ASPARTATE-ASSOCIATED GLYCINE AG-<br>oNISTS. The NMDA-associated glycine receptor is a<br>positive allosteric site on the NMDA rec cGMP (Biggio et al., 1978d). at a<br>b. N-METHYL-D-ASPARTATE-ASSOCIATED GLYCINE AG-<br>and NISTS. The NMDA-associated glycine receptor is a<br>positive allosteric site on the NMDA receptor complex<br>(Johnson and Archer, 1987; Monagha D. N-METHYL-D-ASPARTATE-ASSOCIATED GLYCINE AG-<br>ONISTS. The NMDA-associated glycine receptor is a<br>positive allosteric site on the NMDA receptor complex<br>(Johnson and Archer, 1987; Monaghan et al., 1988) and<br>is analogous with 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 intra-ventr positive allosteric site on the NMDA receptor comple:<br>(Johnson and Archer, 1987; Monaghan et al., 1988) and<br>is analogous with the benzodiazepine/GABA recepto<br>complex (Wood et al., 1989c). Glycine itself, after intra<br>ventri (Johnson and Archer, 1987; Monaghan et al., 1988) and<br>
is analogous with the benzodiazepine/GABA receptor<br>
complex (Wood et al., 1989c). Glycine itself, after intra-<br>
ventricular (Danysz et al., 1989;) or direct intracere is analogous with the benzodiazepine/GABA receptor<br>
complex (Wood et al., 1989c). Glycine itself, after intra-<br>
ventricular (Danysz et al., 1989;) or direct intracerebellar<br>
in<br>
(Rao et al., 1990d) injection, increases ce complex (Wood et al., 1989c). Glycine itself, after intra-<br>ventricular (Danysz et al., 1989;) or direct intracerebellar<br>(Rao et al., 1990d) injection, increases cerebellar cGMP<br>levels. Similarly, D-serine, a stereospecifi ventricular (Danysz et al., 1989;) or direct intracerebellar (Rao et al., 1990d) injection, increases cerebellar cGMP<br>levels. Similarly, D-serine, a stereospecific agonist for the<br>glycine receptor, which is not a substrate (Rao et al., 1990d) injection, increases cerebellar cGMP 19<br>levels. Similarly, D-serine, a stereospecific agonist for the<br>glycine receptor, which is not a substrate for amino acid<br>uptake carriers (Balcar and Johnson, 1973 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 efficac 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). Th 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., 1 pendently increases cerebellar cGMP with an effica<br>approximately one-half that of NMDA (Wood et a<br>1989a). The partial glycine agonist, p-cycloserine (E.<br>mett et al., 1990), also increases cGMP levels after eith<br>parenteral approximately one-half that of NMDA (Wood et al<br>1989a). The partial glycine agonist, D-cycloserine (Em<br>mett et al., 1990), also increases cGMP levels after eithe<br>parenteral or direct intracerebellar drug administration<br>but 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 d 1990).





in a dose-dependent manner (fig. 2). Analyses of the have demonstrated extremely high levels of glycine (Ca-<br>interactions of NMDA with its receptor also suggest that bier and Pessac, 1987). The anatomical proximity of glia EREBELLUM 13<br>
The source of endogenous glycine in vivo requires<br>
further definition; however, studies of cerebellar astroglia<br>
have demonstrated extremely high levels of glycine (Ca-13<br>
The source of endogenous glycine in vivo requires<br>
further definition; however, studies of cerebellar astroglia<br>
have demonstrated extremely high levels of glycine (Ca-<br>
bier and Pessac, 1987). The anatomical proximity The source of endogenous glycine in vivo requires<br>further definition; however, studies of cerebellar astroglia<br>have demonstrated extremely high levels of glycine (Ca-<br>bier and Pessac, 1987). The anatomical proximity of gli The source of endogenous glycine in vivo requires<br>further definition; however, studies of cerebellar astroglia<br>have demonstrated extremely high levels of glycine (Ca-<br>bier and Pessac, 1987). The anatomical proximity of gli further definition; however, studies of cerebellar astroglia<br>have demonstrated extremely high levels of glycine (Ca-<br>bier and Pessac, 1987). The anatomical proximity of glial<br>cells to nerve terminals (Hatten et al., 1984; 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 t of and Fessac, 1567). The anatom<br>cells to nerve terminals (Hatten et<br>Chan-Palay, 1974; Reese et al., 19<br>may be an important pool of glycin<br>of NMDA-mediated neurotransmis<br>c. ENDOGENOUS EXCITATORY A Chan-Palay, 1974; Reese et al., 1985) suggests that this<br>may be an important pool of glycine for the modulation<br>of NMDA-mediated neurotransmission.<br>c. ENDOGENOUS EXCITATORY AMINO ACID RELEASE.<br>Although the identity of EAA

maline- and isoniazid-dependent increases in cerebellar antagonists (Wood et al., 1987, 1989c), NMDA-associ-<br>
CGMP (Biggio et al., 1978d).<br>
b. N-METHYL-D-ASPARTATE-ASSOCIATED GLYCINE AG-<br>
oNISTS. The NMDA-associated glycin c. ENDOGENOUS EXCITATORY AMINO ACID RELEASE.<br>Although the identity of EAA transmitters in the cere-<br>bellum has not been unequivocally demonstrated, phar-<br>macological tools are available to activate EAA-utilizing of NMDA-mediated neufotrafismission.<br>
c. ENDOGENOUS EXCITATORY AMINO ACID RELEASE.<br>
Although the identity of EAA transmitters in the cere-<br>
bellum has not been unequivocally demonstrated, phar-<br>
macological tools are avail exercises and 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 clim climbing fiber inputs to 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 macological tools are available to activate EAA-difficulty<br>pathways. These include harmaline which activates<br>climbing fiber inputs to the cerebellum (Guidotti et al.,<br>1975; Wood et al., 1982) and pentylenetetrazol which<br>i pathways. These include harmanne which activates<br>climbing fiber inputs to the cerebellum (Guidotti et al.,<br>1975; Wood et al., 1982) and pentylenetetrazol which<br>inhibits GABAergic synapses allowing excessive EAA<br>transmissio dose-dependent increases in cerebellar cGMP levels that<br>
are antagonized by competitive NMDA antagonized<br>
are antagonized by competitive NMDA antagonists<br>
(Wood et al., 1982, 1987, 1989c), noncompetitive NMDA<br>
(Wood et al. inhibits GABAergic synapses allowing excessive EAA<br>
transmission (Wood et al., 1990a). These drugs elicit<br>
dose-dependent increases in cerebellar cGMP levels that<br>
are antagonized by competitive NMDA antagonists<br>
(Wood et dose-dependent increases in cerebellar cGMP levels that are antagonized by competitive NMDA antagonists dose-dependent increases in cerebellar cGMP levels that<br>are antagonized by competitive NMDA antagonists<br>(Wood et al., 1982, 1987, 1989c), noncompetitive NMDA<br>antagonists (Wood et al., 1987, 1989c), NMDA-associ-<br>ated glycin are antagonized by competitive NMDA antagonists<br>(Wood et al., 1982, 1987, 1989c), noncompetitive NMDA<br>antagonists (Wood et al., 1987, 1989c), NMDA-associ-<br>ated glycine receptor antagonists (Wood et al., 1989d),<br>and inhibit (Wood et al., 1982, 1987, 1989c), none<br>antagonists (Wood et al., 1987, 1989<br>ated glycine receptor antagonists (W<br>and inhibitors of NO synthase (W<br>Wood, 1990; Wood and Rao, 1990).<br>d. ROLE OF NITRIC OXIDE. The b tagonists (Wood et al., 1987, 1989c), NMDA-associenties (Wood et al., 1989d), displaying receptor antagonists (Wood et al., 1989d), displaying including the biosynthesis of NO synthase (Role of NO synthase (Bredt and Snyde

ated glycine receptor antagonists (Wood et al., 1989d), and inhibitors of NO synthase (Wood et al., 1990b; Wood, 1990; Wood and Rao, 1990).<br>
d. ROLE OF NITRIC OXIDE. The biosynthesis of NO from arginine, via NO synthase (B and initiations of NO synthase (wood et al., 1990b),<br>Wood, 1990; Wood and Rao, 1990).<br>d. ROLE OF NITRIC OXIDE. The biosynthesis of NO<br>from arginine, via NO synthase (Bredt and Snyder,<br>1990), is a signal transduction mechan d. ROLE OF NITRIC OXIDE. The biosynthesis of NO<br>from arginine, via NO synthase (Bredt and Snyder,<br>1990), is a signal transduction mechanism (section III.A)<br>that has been shown to be stimulated by EAA agonists<br>in vitro (Bre d. ROLE OF NITRIC OXIDE. The Diosynthesis of NO<br>from arginine, via NO synthase (Bredt and Snyder,<br>1990), is a signal transduction mechanism (section III.A)<br>that has been shown to be stimulated by EAA agonists<br>in vitro (Bre 1990), is a signal transduction mechanism (section III.A)<br>that has been shown to be stimulated by EAA agonists<br>in vitro (Bredt and Snyder, 1989; Garthwaite et al., 1988,<br>1989a,b). Similarly, the NO synthase inhibitor, N-mo that has been shown to be stimulated by EAA agonists<br>in vitro (Bredt and Snyder, 1989; Garthwaite et al., 1988,<br>1989a,b). Similarly, the NO synthase inhibitor, N-mon-<br>omethyl-L-arginine, has been shown to decrease basal<br>cG In viro (Diedi and Shyder, 1565, Gardiwalde et al., 1566, 1989a,b). Similarly, the NO synthase inhibitor, N-mon-<br>omethyl-L-arginine, has been shown to decrease basal<br>cGMP levels and to block NMDA-, quisqualate-, and<br>kainat 1999a, 9). Similarly, the NO synthase inhibitor, N-mon-<br>
omethyl-L-arginine, has been shown to decrease basal<br>
cGMP levels and to block NMDA-, quisqualate-, and<br>
kainate-dependent increases in cGMP in vivo (Wood et<br>
al., 1 1975; Wood et al., 1982) and pentylenetetrazol which indities GABAergic synspess allowing excessive EAA transmission (Wood et al., 1990a). These drugs elicit dose-dependent increases in cerebellar GGMP levels that are ant cGMP levels and to block NMDA-, quisqualate-, and<br>kainate-dependent increases in cGMP in vivo (Wood et<br>al., 1990b; Wood and Rao, 1990; Wood, 1990; table 4).<br>These data indicate that NO formation is stimulated by<br>all three kainate-dependent increases in cGMP in vivo (Wood et al., 1990); Wood and Rao, 1990; Wood, 1990; table 4).<br>These data indicate that NO formation is stimulated by all three EAA receptor subtypes in vivo and that the diffusi al., 1990b; Wood and Rao, 1990; Wood, 1990; table 4).<br>These data indicate that NO formation is stimulated by<br>all three EAA receptor subtypes in vivo and that the<br>diffusible intercellular messenger, NO, then activates<br>guany These data mulcate that NO formation is stimulated by<br>all three EAA receptor subtypes in vivo and that the<br>diffusible intercellular messenger, NO, then activates<br>guanylate cyclase in a number of cerebellar cell types<br>(sect diffusible intertential messenger, NO, then activates<br>guanylate cyclase in a number of cerebellar cell types<br>(section III.A). The Ca<sup>2+</sup> dependency of NO synthase<br>(Bredt and Snyder, 1990) is consistent with prior reports<br> (section III.A). The Ca<sup>2+</sup> dependency of N<br>(Bredt and Snyder, 1990) is consistent with p<br>that pharmacological activation of cerebellar<br>a variety of mechanisms, was  $Ca^{2+}$  dependen<br>These studies encompassed cerebellar sl (Bredt and Snyder, 1990) is consistent with prior reports<br>that pharmacological activation of cerebellar cGMP, via<br>a variety of mechanisms, was  $Ca^{2+}$  dependent.<br>These studies encompassed cerebellar slices (Ferrenthat pharmacological activation of cerebellar cGMP, via

that pharmacological activation of cerebellar cGMP,<br>a variety of mechanisms, was Ca<sup>2+</sup> dependent.<br>These studies encompassed cerebellar slices (Fer<br>delli et al., 1973), cultured granule cells (Novelli<br>Henneberry, 1987), an a variety of mechanisms, was  $Ca^{2+}$  dependent.<br>
These studies encompassed cerebellar slices (Ferren-<br>
delli et al., 1973), cultured granule cells (Novelli and<br>
Henneberry, 1987), and in vivo studies with intracere-<br>
bell These studies encompasse<br>delli et al., 1973), cultured<br>Henneberry, 1987), and in v<br>bellar injections of the Ca<sup>2+</sup><br>Wood, unpublished results).<br>e. ROLE OF NORADRENERG Henneberry, 1987), and in vivo studies with intracere-<br>bellar injections of the Ca<sup>2+</sup> antagonist, diltiazem (P. L.<br>Wood, unpublished results).<br>e. ROLE OF NORADRENERGIC AFFERENTS. The cerebel-

Henneberry, 1987), and in vivo studies with intracere-<br>bellar injections of the Ca<sup>2+</sup> antagonist, diltiazem (P. L.<br>Wood, unpublished results).<br>e. ROLE OF NORADRENERGIC AFFERENTS. The cerebel-<br>lum receives an extensive nor e. ROLE OF NORADRENERGIC AFFERENTS. The cere<br>lum receives an extensive noradrenergic fiber input f<br>the locus coeruleus and other pontine noradrenergic<br>clei (Bloom et al., 1971; Olsen and Fuxe, 1971). Addit<br>ally, biochemica e. ROLE OF NORADRENERGIC AFFERENTS. The cereber-<br>lum receives an extensive noradrenergic fiber input from<br>the locus coeruleus and other pontine noradrenergic nu-<br>clei (Bloom et al., 1971; Olsen and Fuxe, 1971). Addition-<br>a 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 norepi 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 norepi clei (Bloom et al., 1971; Olsen and Fuxe, 1971). Additionally, biochemical studies with cerebellar slices have<br>shown that presynaptic NMDA/PCP receptors regulate<br>norepinephrine release from these nerve endings in the<br>cere shown that presynaptic NMDA/PCP receptors regulate<br>norepinephrine release from these nerve endings in the<br>cerebellum (Yi et al., 1988). In vivo, norepinephrine and<br>selective  $\alpha_1$ -noradrenergic agonists have been shown t

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

Drug Treatment $(\mu$ g, intracerebellar) [mg/kg, sc]	cGMP (% control)	1.0 <sub>1</sub> हु 0.5	
<b>NMMA (10)</b>	68		
<b>NMMA</b> (25)	65	$0.0 -$ $-0.5$	
<b>NMMA (50)</b>	53		
<b>NMMA (100)</b>	54		
$NMMA (100) + L-arginine (200)$	100	$-1.0 -$	
L-Arginine (200)	100	0.7	
Quisqualate (5)	1184		
Quisqualate $(5) + NMMA (100)$	228	FIG. 3. Logit-l	
Kainate (0.3)	1199		
Kainate (0.3) + NMMA (100)	482	ebellar cGMP ind	
D-Serine (200)	279	and the noncomp min).	
D-Serine (200) + NMMA (25)	100		
D-Serine (200) + NMMA (100)	100		
Harmaline [100]	935	D-serine-, har increases in ce	
Harmaline $[100] + NMMA (50)$	277		
<b>PTZ</b> [50]	395		
$PTZ [50] + NMMA (50)$	100	petitive NMD	

PTZ  $[50]$  + NMMA  $(50)$  100<br>
\* Abbreviations: NMMA, N-monomethyl-L-arginine; PTZ, pentyle-<br>
netetrazol (Wood et al., 1990b). Intracerebellar antagonists treatments<br>
were coinjections with agonist treatments which were al netetrazol (Wood et al., 1990b). Intracerebellar antagonists treatments<br>were coinjections with agonist treatments which were all 10 min prior<br>to microwave fixation.<br>increase cerebellar cGMP (Haidamous et al., 1980),

whereas  $\alpha_1$  antagonists decrease cGMP levels (Chung, metetrazol (Wood et al., 1990b). Intracerebellar antagonists treatments<br>were coinjections with agonist treatments which were all 10 min prior<br>to microwave fixation.<br>increase cerebellar cGMP (Haidamous et al., 1980),<br>where were comjections with agonist treatments which were all 10 min prior<br>to microwave fixation.<br>increase cerebellar cGMP (Haidamous et al., 1980),<br>whereas  $\alpha_1$  antagonists decrease cGMP levels (Chung,<br>1983; Haidamous et al. increase cerebellar cGMP (Haidamous et al., 1980)<br>whereas  $\alpha_1$  antagonists decrease cGMP levels (Chung<br>1983; Haidamous et al., 1980). These data suggest that<br>there might be a tonic noradrenergic input which posi-<br>tively increase cerebellar cGMP (Haidamous et al., 1980),<br>whereas  $\alpha_1$  antagonists decrease cGMP levels (Chung,<br>1983; Haidamous et al., 1980). These data suggest that<br>there might be a tonic noradrenergic input which posi-<br>tive whereas  $\alpha_1$  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  $\alpha_1$  receptor subty 1983; Haidamous et al., 1980). These data suggest that<br>there might be a tonic noradrenergic input which posi-<br>tively modulates cGMP levels via an  $\alpha_1$  receptor subtype<br>and that the terminals of these noradrenergic affer these might be a tomc horal energic mput which positively modulates cGMP levels via an  $\alpha_1$  receptor subtype cand that the terminals of these noradrenergic afferent refibers can be positively driven by NMDA receptor ago fibers can be positively driven by NMDA receptor ago-<br>nists. Such a hypothesis is supported by the observations<br>competitive NMDA antagonists, does not alter basal<br>that the nonselective  $\alpha_1$  antagonist, clozapine, and th nists. Such a hypothesis is supported by the observations mists. Such a hypothesis is supported by the observations contact the nonselective  $\alpha_1$  antagonist, clozapine, and the cesselective antagonist, WB-4101, both can antagonize the this ability of NMDA, D-serine, harmaline, that the nonselective  $\alpha_1$  antagonist, clozapine, and the selective antagonist, WB-4101, both can antagonize the ability of NMDA, D-serine, harmaline, and pentylenete-<br>trazol to increase cGMP levels (Rao et al., 1990h; selective antagonist, WB-4101, both can antagonize the<br>ability of NMDA, D-serine, harmaline, and pentylenete-<br>trazol to increase cGMP levels (Rao et al., 1990h; Wood<br>and Rao, 1990). Of significance, these  $\alpha_1$  antagonis ability of NMDA, D-serine, harmaline, and pentylenete-<br>trazol to increase cGMP levels (Rao et al., 1990h; Wood<br>and Rao, 1990). Of significance, these  $\alpha_1$  antagonists<br>were unable to modify quisqualate-dependent increase trazol to increase cGMP levels (Rao et al., 1990h; Wood<br>and Rao, 1990). Of significance, these  $\alpha_1$  antagonists<br>were unable to modify quisqualate-dependent increases<br>in cGMP (Rao et al., 1990h), which would be consisten and Rao, 1990). Of significance, these  $\alpha_1$  antagonists<br>were unable to modify quisqualate-dependent increases<br>in cGMP (Rao et al., 1990h), which would be consistent<br>with the presence of quisqualate receptors on Purkinje were unable to modify quisqualate-dependent increases tag<br>in cGMP (Rao et al., 1990h), which would be consistent l<br>with the presence of quisqualate receptors on Purkinje NIS<br>cell dendrites and not on noradrenergic nerve en in cGMP (Rao et al., 1990h), which would be consistent<br>with the presence of quisqualate receptors on Purkinje<br>cell dendrites and not on noradrenergic nerve endings<br>q(Olson et al., 1987). These data are also consistent with with the presence of quisqualate receptors on Purkinje<br>cell dendrites and not on noradrenergic nerve endings<br>(Olson et al., 1987). These data are also consistent with<br>earlier electrophysiological studies from which it was<br> cell dendrites and not on noradrenergic nerve endings<br>(Olson et al., 1987). These data are also consistent with<br>earlier electrophysiological studies from which it was<br>concluded that suppression of cerebellar Purkinje cell<br> (Olson et al., 1987). These data are also consistent with 2,3-c earlier electrophysiological studies from which it was ebell concluded that suppression of cerebellar Purkinje cell How firing induced by PCP agonists was due earlier electrophysiological studies from which it<br>concluded that suppression of cerebellar Purkinje<br>firing induced by PCP agonists was due to presyna<br>inhibition of norepinephrine release in the cerebel<br>(Marwaha et al., 19 firing induced by PCP agonists was due to presynaptic<br>inhibition of norepinephrine release in the cerebellum<br>(Marwaha et al., 1980, 1981; Wang and Lee, 1989).<br>f. COMPETITIVE AND NONCOMPETITIVE N-METHYL-D-

**ASPARTATE ANTAGONISTS.** A number of linear and responsive in the cerebellum at the (Marwaha et al., 1980, 1981; Wang and Lee, 1989). 1981.<br>
ASPARTATE ANTAGONISTS. A number of linear and rigid and phosphonic acid analogues inhibition of norepinephrine release in the cerebellum at the (Marwaha et al., 1980, 1981; Wang and Lee, 1989). 1989;<br>f. COMPETITIVE AND NONCOMPETITIVE N-METHYL-D-<br>ASPARTATE ANTAGONISTS. A number of linear and rigid and<br>ph Marwaha et al., 1980, 1981; Wang and Lee, 1989).<br>
f. COMPETITIVE AND NONCOMPETITIVE N-METHYL-D-<br>
ASPARTATE ANTAGONISTS. A number of linear and rigid<br>
phosphonic acid analogues which are competitive NMDA<br>
antagonists (Czucz f. COMPETITIVE AND NONCOMPETITIVE N-METHYL-D-<br>ASPARTATE ANTAGONISTS. A number of linear and rigid and<br>phosphonic acid analogues which are competitive NMDA ad<br>antagonists (Czuczwar and Meldrum, 1982; Lehmann et bu<br>al., 1988 phosphonic acid analogues which are competitive NMDA administration, do not alter basal cerebellar cGMP levels<br>antagonists (Czuczwar and Meldrum, 1982; Lehmann et but do antagonize the effects of NMDA and quisqualate<br>al., phosphonic acid analogues which are competitive NMDA ad<br>antagonists (Czuczwar and Meldrum, 1982; Lehmann et bu<br>al., 1988b, 1987) have been examined and all were found re<br>to dose dependently decrease basal cGMP levels (fig. antagonists (Czuczwar and Meldrum, 1982; Lehmann et bual., 1988b, 1987) have been examined and all were found red to dose dependently decrease basal cGMP levels (fig. 3), 19<br>thereby demonstrating their ability to antagoniz al., 1988b, 1987) have been examined and all were found rector dose dependently decrease basal cGMP levels (fig. 3), 19<br>thereby demonstrating their ability to antagonize the hasendogenously released EAA neurotransmitter(s) to dose dependently decrease basal cGMP levels (fig. 3),<br>thereby demonstrating their ability to antagonize the<br>endogenously released EAA neurotransmitter(s) in the<br>cerebellum (Wood et al., 1982, 1987, 1989c, 1990a; Wood<br>an



0.7 1.0 10.0<br>LOG DOSE<br>FIG. 3. Logit-log dose-response curves for decrements in basal cer-<br>ebellar cGMP induced by the competitive NMDA antagonist, (CPP),<br>and the noncompetitive NMDA receptor antagonist, tiletamine (30 LOG DOSE<br>FIG. 3. Logit-log dose-response curves for decrements in basal cer-<br>ebellar cGMP induced by the competitive NMDA antagonist, (CPP),<br>and the noncompetitive NMDA receptor antagonist, tiletamine (30<br>min). min). ebellar cGMP induced by the competitive NMDA antagon<br>and the noncompetitive NMDA receptor antagonist, tile<br>min).<br>D-serine-, harmaline-, and pentylenetetrazol-de<br>increases in cerebellar cGMP (tables 5 and 6).

and the honcompetitive NMDA receptor antagonist, thetamine (30 min).<br>
D-serine-, harmaline-, and pentylenetetrazol-dependent<br>
increases in cerebellar cGMP (tables 5 and 6). Noncom-<br>
petitive NMDA antagonists, which act at D-serine-, harmaline-, and pentylenetetrazol-dependent<br>increases in cerebellar cGMP (tables 5 and 6). Noncom-<br>petitive NMDA antagonists, which act at the negatively<br>coupled PCP receptor component of the NMDA receptor<br>compl D-serine-, harmaline-, and pentylenetetrazol-dependencreases in cerebellar cGMP (tables 5 and 6). Nonco<br>petitive NMDA antagonists, which act at the negative<br>coupled PCP receptor component of the NMDA recep<br>complex (Wong et petitive NMDA antagonists, which act at the negatively<br>coupled PCP receptor component of the NMDA receptor<br>complex (Wong et al., 1986), also decrease basal cerebel-<br>lar cGMP levels (fig. 3) in a dose-dependent manner coupled PCP receptor component of the NMDA receptor<br>complex (Wong et al., 1986), also decrease basal cerebel-<br>lar cGMP levels (fig. 3) in a dose-dependent manner<br>(Wood et al., 1987, 1989a,c; Wood and Rao, 1990). These<br>agen complex (Wong et al., 1986), also decrease basal cerebelcomplex (Wong et al., 1986), also decrease basal cerebe<br>lar cGMP levels (fig. 3) in a dose-dependent manne<br>(Wood et al., 1987, 1989a,c; Wood and Rao, 1990). Thes<br>agents also antagonize the actions of D-serine, NMDA<br>harmali ar COMP leven<br>(Wood et al., 198<br>agents also anta<br>harmaline, and p<br>ate or quisqualat<br>g. N-METHYL-1 (wood et al., 1967, 1969a, c; wood and rao, 1990). I hese<br>agents also antagonize the actions of D-serine, NMDA,<br>harmaline, and pentylenetetrazol but not those of kain-<br>ate or quisqualate.<br>g. N-METHYL-D-ASPARTATE-ASSOCIATED

harmaline, and pentylenetetrazol but not those of kainate or quisqualate.<br>
g. N-METHYL-D-ASPARTATE-ASSOCIATED GLYCINE RECEPTOR ANTAGONISTS. The NMDA-associated glycine<br>
receptor antagonist, HA-966 (Bonta et al., 1971; Meno ate or quisqualate.<br>
g. N-METHYL-D-ASPARTATE-ASSOCIATED GLYCINE RE<br>
CEPTOR ANTAGONISTS. The NMDA-associated glycine<br>
receptor antagonist, HA-966 (Bonta et al., 1971; Menon<br>
1981; Wood et al., 1989d), unlike competitive and g. N-METHYL-D-ASPARTATE-ASSOCIATED GLYCINE RE-<br>CEPTOR ANTAGONISTS. The NMDA-associated glycine<br>receptor antagonist, HA-966 (Bonta et al., 1971; Menon,<br>1981; Wood et al., 1989d), unlike competitive and non-<br>competitive NMDA CEPTOR ANTAGONISTS. The NMDA-associated glycine<br>receptor antagonist, HA-966 (Bonta et al., 1971; Menon,<br>1981; Wood et al., 1989d), unlike competitive and non-<br>competitive NMDA antagonists, does not alter basal<br>cerebellar c 1981; Wood et al., 1989d), unlike competitive and non-1981; Wood et al., 1989d), unlike competitive and i<br>competitive NMDA antagonists, does not alter b<br>cerebellar cGMP levels (Wood et al., 1989c). Howe<br>this agent is able to antagonize the increases in cG<br>elicited by NMDA, Dcompetitive NMDA antagonists, does not alter be<br>cerebellar cGMP levels (Wood et al., 1989c). Howev<br>this agent is able to antagonize the increases in cGl<br>elicited by NMDA, D-serine, harmaline, and pentyle<br>tetrazol (table 6) 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 pentylene-tetrazol (table 6). Similar to competitive and noncompetitiv this agent is able to antagonize the increase<br>elicited by NMDA, D-serine, harmaline, and<br>tetrazol (table 6). Similar to competitive an<br>petitive NMDA antagonists, this agent is un<br>tagonize the effects of kainate or quisqual cited by NMDA, D-serine, harmatine, and pentyler<br>trazol (table 6). Similar to competitive and noncol<br>titive NMDA antagonists, this agent is unable to a<br>gonize the effects of kainate or quisqualate.<br>h. NONSELECTIVE EXCITATO

Letrazof (table 6). Similar to competitive and non<br>petitive NMDA antagonists, this agent is unable to<br>tagonize the effects of kainate or quisqualate.<br>h. NONSELECTIVE EXCITATORY AMINO ACID ANT<br>NISTS. The nonselective EAA an petitive NMDA antagonists, this agent is unatagonize the effects of kainate or quisqualate.<br>
h. NONSELECTIVE EXCITATORY AMINO ACII<br>
NISTS. The nonselective EAA antagonists, 6<br>
quinoxaline-2,3-dione and 6-nitro,7-cyanoqu<br>
2 Example the effects of Kalinate of quisqualate.<br>
h. NONSELECTIVE EXCITATORY AMINO ACID ANTAGO-<br>
NISTS. The nonselective EAA antagonists, 6,7-dinitro-<br>
quinoxaline-2,3-dione, antagonize the actions of quisqualate on cer-<br>
e NISTS. The nonselective EAA antagonists, 6,7-dinitro-<br>quinoxaline-2,3-dione and 6-nitro,7-cyanoquinoxaline-<br>2,3-dione, antagonize the actions of quisqualate on cer-<br>ebellar cGMP (Rao et al., 1990e; Wood et al., 1989d).<br>Ho 2,3-dione, antagonize the actions of quisqualate on cerebellar cGMP (Rao et al., 1990e; Wood et al., 1989d).<br>However, these agents also block D-serine and NMDA actions, presumably via their potent antagonist actions at the 2,3-ulone, antagonize the actions of quisquantie on cer-<br>
ebellar cGMP (Rao et al., 1990e; Wood et al., 1989d).<br>
However, these agents also block D-serine and NMDA<br>
actions, presumably via their potent antagonist actions<br> However, these agents also block D-serine and NMDA<br>actions, presumably via their potent antagonist actions<br>at the NMDA-associated glycine receptor (Kessler et al.,<br>1989; Rao et al., 1990e; table 6).<br>i. POLYAMINES. The endo

actions, presumably via their potent antagonist action<br>at the NMDA-associated glycine receptor (Kessler et al.<br>1989; Rao et al., 1990e; table 6).<br>i. POLYAMINES. The endogenous polyamines spermin<br>and spermidine (table 6), a at the NMDA-associated glycine receptor (Kessler et al., 1989; Rao et al., 1990e; table 6).<br>
i. POLYAMINES. The endogenous polyamines spermine<br>
and spermidine (table 6), after direct intracerebellar<br>
administration, do not 1989; Kao et al., 1990e; table 6).<br>i. POLYAMINES. The endogenous polyamines spermine<br>and spermidine (table 6), after direct intracerebellar<br>administration, do not alter basal cerebellar cGMP levels<br>but do antagonize the ef receptor activation, do not alter basal cerebellar cGMP levels<br>administration, do not alter basal cerebellar cGMP levels<br>but do antagonize the effects of NMDA and quisqualate<br>receptor activation (Rao et al., 1990b,c; Wood administration, do not alter basal cerebellar cGMP levels administration, do not alter basal cerebellar cGMP levels<br>but do antagonize the effects of NMDA and quisqualate<br>receptor activation (Rao et al., 1990b,c; Wood and Rao,<br>1990) as well as endogenous EAA release evoked by<br>harm receptor activation (Rao et al., 1990b,c; Wood and Ra<br>1990) as well as endogenous EAA release evoked lammaline (Rao et al., 1990c). This nonselective profit<br>was suggested to possibly involve polyamine-depende<br>decreases in 990) as well as endogenous EAA release evoked by<br>urmaline (Rao et al., 1990c). This nonselective profile<br>as suggested to possibly involve polyamine-dependent<br>creases in intracellular calcium (Rao et al., 1990c).<br>j. SIGMA L



\* Agonist treatments included: apomorphine (Apo) a dopamine agonist; amphetamine (Amph) a dopamine releaser; thyropropin-releasing CCK Yes Yes Yes Yes Yes Yes No - No<br>CPP - Yes - Yes Yes Yes Yes Yes Yes Yes Yes - Yes<br>Kainate - - - - Yes Yes Yes Yes Yes Yes Yes<br>Agonist treatments included: apomorphine (Apo) a dopamine agonist; amphetamine (Amph) a dopa (Picro) as a GABA-A antagonist; isoniazid (laos) as an inhibitor of GABA synthesis; and pentylesetetrazol (PTZ) as a convulsant; -, not tested. **<sup>t</sup>** Antagonist: 3-acetylpyridise lesions of inferior olive to interrupt climbing fibers (Biggio et a!., l977c, d; Guidotti et a!., 1975; Mailman et

urate-omaing site<br>3 19755 to antagon<br>by granular cells (F<br>TABLE 6<br>increases in mouse V. Amount is the competitive NMDA and Kuressen (1989), CPP, AFS, AFP or COS 19755 to antagonist control (ERI) and antagonist behind the competitive NMDA and CHI and <sup>\*</sup> 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) (Picro) as a GABA-A antagonist; isoniazid (Ison) as an inhibitor of GABA synthesis; and pentylenetetrazol (PTZ) as a convulsant; -, not tested.<br>† Antagonist: 3-acetylpyridine lesions of inferior olive to interrupt climbin (Picro) as a GABA-A antagonist; isoniazid (Ison) as an inhibitor of GABA synthesis; and pentylenetetrazol (PTZ) as a convulsant; -, not tested.<br>
† Antagonist: 3-acetylpyridine lesions of inferior olive to interrupt climbi 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 dopami were reversed; propranolol to block  $\beta$ -adrenergic receptors (Narumi et al., 1983); atropine or trihhexyphenidyl to block muscarinic receptors (Biggio et al., 1976; d; Burkard et al., 1985; Mailman et al., 1979; Opmeer e (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.,





Polyamines Yes Yes Yes Yes Yes Yes NT<br>Sigma ligands Yes No NT Yes NT NT<br>Ifenprodil Yes Yes NT NT<br>\*Competitive NMDA antagonists: CPP and CGS 19755 (Lehmann et al., 1987; 1988a, b; Wood et al., 1987); noncompetitive NMDA<br>ant antagonist (Bonta et al., 1971; Wood et al., 1989a, c, d, 1990a; Wood and Rao, 1990); Rolyamines: spermine and spermidine (Rao et al., 1989a, c, d, 1990a; Wood and Rao, 1990); sonselective EAA antagonists: 6,7-dinitroquino FESTER THESTER THESTER THESTER THESTER THESTER THESTER THESTER THESTER TO THESTER THESTER TO THESTER THESTER TO THESTER THESTER TO THESTER THESTER THESTER TO THESTER THESTER THESTER CONDELLED THESTER THESTER THESTER CONDEL \* Competitive NMDA antagonists: CPP and CGS 19755 (Lehmann et al., 1987; 1988a, b; Wood et al., 1987); noncompetitive NMDA<br>antagonists: MK-801, PCP, dexoxadrol (Lehmann et al., 1986; Lehmann and Wood, 1988; Wood et al., 19 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 opipr Rao, 1990); nonselective EAA antagonists: 6,7-dinitroquinoxaline a<br>Rocod and Rao, 1990); Polyamines: spermine and spermidine (Rao<br>d opipramol (Rao et al., 1990a; Wood and Rao 1990); ifenprodil, mix<br>1988, 1999; Rao et al.,

6-nitro,7-cyanoquinoxaline-2,3-dione (Birch et al., 1988; Rao et al., 1990e; Wood, al., 1990b, c; Wood and Rao, 1990); sigma receptor ligands: BMY 14802 and operation of sigma/polyamine receptor ligands: ifenprodil and SL all, 1990b, c; wood and Rao, 1990); sigma receptor ligands: BMT 14802 a<br>sigma/polyamine receptor ligands: ifenprodil and SL 76002 (Carter et al.<br>ligands have been observed to antagonize increases in<br>cerebellar cGMP elicite Signa, polyanmic receptor ngands. henprodu and SD 70002 (Carter eligands have been observed to antagonize increases is cerebellar cGMP elicited by activation of NMDA an NMDA-associated glycine receptors (Rao et al., 1990a, ligands have been observed to antagonize increases in recerebellar cGMP elicited by activation of NMDA and for NMDA-associated glycine receptors (Rao et al., 1990a,f; Wood and Rao, 1990). BMY 14802, an apparently selective cerebellar cGMP elicited by activation of NMDA and<br>NMDA-associated glycine receptors (Rao et al., 1990a,f;<br>Wood and Rao, 1990). BMY 14802, an apparently selec-<br>tive sigma ligand, although slightly elevating basal cGMP<br>leve NMDA-associated glycine receptors (Rao et al., 1990a,f;<br>Wood and Rao, 1990). BMY 14802, an apparently selective sigma ligand, although slightly elevating basal cGMP T<br>levels, also selectively antagonizes NMDA-dependent inc Wood and Rao, 1990). BMY 14802, an apparently selective sigma ligand, although slightly elevating basal cGMP<br>levels, also selectively antagonizes NMDA-dependent increases in cGMP without altering cGMP responses to be<br>quisq tive sigma ligand, although slightly elevating basal cGM<br>levels, also selectively antagonizes NMDA-dependent increases in cGMP without altering cGMP responses to<br>quisqualate. This effect on NMDA receptor action<br>centrally m levels, also selectively antagonizes NMDA-dependent in-<br>creases in cGMP without altering cGMP responses to bellun<br>quisqualate. This effect on NMDA receptor action is erals<br>centrally mediated as evidenced by efficacy after creases in cGMP without altering cGMP responses to<br>quisqualate. This effect on NMDA receptor action is<br>centrally mediated as evidenced by efficacy after intra-<br>ventricular injections (Rao et al., 1990a); however, BMY<br>14802 quisqualate. This effect on NMDA receptor action is erals to the granule cell layer (Palay and Chan-Palay, centrally mediated as evidenced by efficacy after intra-<br>ventricular injections (Rao et al., 1990a); however, BMY t centrally mediated as evidenced by efficacy after intra-

d opipramol (Rao et al., 1990a; Wood and Rao 1<br>1988, 1999; Rao et al., 1989; Wood and Rao, 19<br>receptor modulation of NMDA recept<br>fore, requires more intense investigati et al., 1989; Wood and Rao, 1990). NT, not tests<br>
ulation of NMDA receptor function, the<br>
more intense investigation.<br> **IV. Climbing Fiber System**<br>
ng fiber pathway is a system with a disc

IV. Climbing Fiber System<br>The climbing fiber pathway is a system with a discrete origin in the inferior intense investigation.<br>
IV. Climbing Fiber System<br>
The climbing fiber pathway is a system with a discrete<br>
origin in the inferior olive, which ascends into the cere-<br>
bellum to innervate Purkinje cel IV. Climbing Fiber System<br>The climbing fiber pathway is a system with a discretion<br>origin in the inferior olive, which ascends into the cell<br>bellum to innervate Purkinje cells and also sends colla<br>erals to the granule cell IV. Climbing Fiber System<br>The climbing fiber pathway is a system with a discret<br>origin in the inferior olive, which ascends into the cere<br>bellum to innervate Purkinje cells and also sends collat<br>erals to the granule cell l I he climbing inter pathway is a system with a discrete origin in the inferior olive, which ascends into the cere-<br>bellum to innervate Purkinje cells and also sends collat-<br>erals to the granule cell layer (Palay and Chan-P bellum 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.<br>The climbing fiber s llum to innervate Purkinje cells and also sends collat-<br>als to the granule cell layer (Palay and Chan-Palay,<br>74; fig. 1). As discussed in section III.A, this appears<br>be an EAA-utilizing pathway.<br>The climbing fiber system i erals 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.<br>The climbing fiber system is unique in that it can be selectively activated

1974; fig. 1). As discussed in section III.A, this appears to be an EAA-utilizing pathway.<br>
The climbing fiber system is unique in that it can be selectively activated by the alkaloid, harmaline (Biggio et al., 1977c; Guid

16<br>1989c, 1990a), and is lesioned by the toxin, 3-acetyl<br>idine (Balaban, 1985; Guidotti et al., 1975). The act woo woo<br>1989c, 1990a), and is lesioned by the toxin, 3-acetylpyr-<br>idine (Balaban, 1985; Guidotti et al., 1975). The actions<br>of harmaline involve enhanced firing of the inferior olive wood 1989c, 1990a), and is lesioned by the toxin, 3-acetylpyr-<br>ightharmaline (Balaban, 1985; Guidotti et al., 1975). The actions sign<br>of harmaline involve enhanced firing of the inferior olive the<br>(LaMarre et al., 1971) wh 1989c, 1990a), and is lesioned by the toxin, 3-acetylpyr-<br>
idine (Balaban, 1985; Guidotti et al., 1975). The actions si<br>
of harmaline involve enhanced firing of the inferior olive<br>
(LaMarre et al., 1971) which, in turn, le 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). Th (LaMarre et al., 1971) which, in turn, leads to increased (LaMarre et al., 1971) which, in turn, leads to increased<br>cerebellar cGMP levels (Biggio et al., 1977c; Guidotti et<br>al., 1975; Wood et al., 1982, 1989c, 1990a). The actions<br>of harmaline involve increased cGMP in both the v cerebellar cGMP levels (Biggio et al., 1977c; Guidotti et 1977). S<br>al., 1975; Wood et al., 1982, 1989c, 1990a). The actions activity<br>of harmaline involve increased cGMP in both the vermis cGMP s<br>and hemispheres of the cere al., 1975; Wood et al., 1982, 1989c, 1990a). The actions action of harmaline involve increased cGMP in both the vermis cGl and hemispheres of the cerebellum (Guidotti et al., 1975; (Bi Rubin and Ferrendelli, 1977), with ap of harmaline involve increased cGMP in both the vermis<br>and hemispheres of the cerebellum (Guidotti et al., 1975;<br>Rubin and Ferrendelli, 1977), with approximately 80%<br>of the tissue change occurring in the molecular layer an and hemispheres of the cerebellum (Guidotti et al., 197<br>Rubin and Ferrendelli, 1977), with approximately 80<br>of the tissue change occurring in the molecular layer are<br>20% in the granular layer (Rubin and Ferrendelli, 1977<br>T Rubin and Ferrendelli, 1977), with approximately 80%<br>of the tissue change occurring in the molecular layer and<br>20% in the granular layer (Rubin and Ferrendelli, 1977).<br>The mechanism of action of harmaline remains unde-<br>fin of the tissue change occurring in the molecular layer and 20% in the granular layer (Rubin and Ferrendelli, 1977).<br>The mechanism of action of harmaline remains unde-<br>fined at this time, but it is not a result of its monoam 20% in the granular layer (Rubin and Ferrendelli, 1977). dott<br>The mechanism of action of harmaline remains unde-<br>fined at this time, but it is not a result of its monoamine ebel<br>oxidase-inhibiting properties because other The mechanism of action of harmaline remains unde-<br>fined at this time, but it is not a result of its monoamine<br>oxidase-inhibiting properties because other monoamine<br>oxidase inhibitors, such as pargyline and deprenyl, do<br>no fined at this time, but it is not a result of its monoamine<br>oxidase-inhibiting properties because other monoamine<br>oxidase inhibitors, such as pargyline and deprenyl, do<br>not alter cerebellar cGMP (Costa et al., 1974; Mao et oxidase inhibiting properties because other monoamine<br>oxidase inhibitors, such as pargyline and deprenyl, do<br>not alter cerebellar cGMP (Costa et al., 1974; Mao et al.<br>1974a). No benzodiazepine receptor involvement is evide oxidase inhibitors, such as pargyline and deprenyl, not alter cerebellar cGMP (Costa et al., 1974; Mao et a<br>1974a). No benzodiazepine receptor involvement is event, because the benzodiazepine receptor antagonis<br>flumazenil, not alter cerebellar cGMP (Costa et al., 1974; Mao et al.<br>1974a). No benzodiazepine receptor involvement is evident, because the benzodiazepine receptor antagonist<br>flumazenil, does not alter the effects of harmaline (Moh<br>l 1974a). No benzodiazepine receptor involvement is evident, because the benzodiazepine receptor antagonist, 1<br>flumazenil, does not alter the effects of harmaline (Mohler et al., 1981) and the actions of harmaline are inde-<br> dent, because the benzodiazepine receptor antagonist,<br>flumazenil, does not alter the effects of harmaline (Mohler et al., 1981) and the actions of harmaline are inde-<br>pendent of motor activity changes as examined in d-<br>tub mazenil, does not alter the effects of harmaline (Moh-<br>
identical studies (table 7) and the actions of harmaline are inde-<br>
indent of motor activity changes as examined in d-<br>
bocurarine-paralyzed animals (Lundberg et al.

ler et al., 1981) and the actions of harmaline are independent of motor activity changes as examined in d-<br>tubocurarine-paralyzed animals (Lundberg et al., 1979).<br>In a number of pharmacological studies (table 5), the<br>acti pendent of motor activity changes as examined in d-<br>tubocurarine-paralyzed animals (Lundberg et al., 1979).<br>In a number of pharmacological studies (table 5), the<br>actions of harmaline have been shown to be antagonized<br>by di tubocurarine-paralyzed animals (Lundberg et al., 19'<br>In a number of pharmacological studies (table 5),<br>actions of harmaline have been shown to be antagon<br>by diazepam and pentobarbital (Dodson and John:<br>1979), presumably vi In a number of pharmacological studies (table 5), the<br>actions of harmaline have been shown to be antagonized<br>by diazepam and pentobarbital (Dodson and Johnson,<br>1979), presumably via enhanced GABAergic transmis-<br>sion within actions of harmaline have been shown to be antagonized A. by diazepam and pentobarbital (Dodson and Johnson, 1979), presumably via enhanced GABAergic transmision within the cerebellum (section III. B.1); competitive cell by diazepam and pentobarbital (Dodson and Johnson,<br>1979), presumably via enhanced GABAergic transmistion<br>sion within the cerebellum (section III. B.1); competitive<br>NMDA receptor antagonists such as CPP (Lehmann and<br>wood, 1 1979), presumably via enhanced GABAergic transmis-<br>sion within the cerebellum (section III. B.1); competitive<br>NMDA receptor antagonists such as CPP (Lehmann and<br>Wood, 1988; Lehmann et al., 1987) and CGS 19755<br>(Lehmann et a sion within the cerebellum (section III. B.1); competit NMDA receptor antagonists such as CPP (Lehmann a Wood, 1988; Lehmann et al., 1987) and CGS 197 (Lehmann et al., 1988a,b); noncompetitive NMDA atagonists (Wood et al., NMDA receptor antagonists such as CPP (Lehmann and<br>Wood, 1988; Lehmann et al., 1987) and CGS 19755<br>(Lehmann et al., 1988a,b); noncompetitive NMDA an-<br>tagonists (Wood et al., 1987); antagonists of NMDA-<br>associated glycine r Wood, 1988; Lehmann et al., 1987) and CGS 19755<br>(Lehmann et al., 1988a,b); noncompetitive NMDA an-<br>tagonists (Wood et al., 1987); antagonists of NMDA-<br>associated glycine receptors (Wood et al., 1989d), pre-<br>sumably via inh (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 cere tagonists (Wood et al., 1987); antagonists of NMDA-<br>associated glycine receptors (Wood et al., 1989d), pre-<br>sumably via inhibition of NMDA-mediated transmission<br>within the cerebellum (section III.B.6); CCK fragments<br>is (W associated glycine receptors (Wood et al., 1989d), 1<br>sumably via inhibition of NMDA-mediated transmiss<br>within the cerebellum (section III.B.6); CCK fragme<br>(Wood et al., 1988b, 1989) and the CCK-like pepr<br>caerulein (Kageyam sumably via inhibition of NMDA-mediated transmission<br>within the cerebellum (section III.B.6); CCK fragments<br>(Wood et al., 1988b, 1989) and the CCK-like peptide<br>caerulein (Kageyama and Kurosawa, 1989), via extracer-<br>ebellar within the cerebellum (section III.B.6); CCK fragments ity<br>
(Wood et al., 1988b, 1989) and the CCK-like peptide<br>
caerulein (Kageyama and Kurosawa, 1989), via extracer-<br>
shellar actions (section V.B.4); alcohol (Rappaport caerulein (Kageyama and Kurosawa, 1989), via extracer-<br>
ebellar actions (section V.B.4); alcohol (Rappaport et al.,  $1.$  Dopaminergic modulators. A number of early studies<br>
1984; section III.B.4); 3-acetylpyridine lesions caerulein (Kageyama and Kurosawa, 1989), via extrace<br>ebellar actions (section V.B.4); alcohol (Rappaport et a<br>1984; section III.B.4); 3-acetylpyridine lesions of tl<br>climbing fiber pathway (Biggio et al., 1977a; Guidotti<br>al ebellar 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); si 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; climbing fiber pa<br>al., 1975; Mailma<br>tor ligands (Rao<br>section III.B.6.j);<br>section III.B.g.i).<br>In contrast, th 1975; Mailman et al., 1979; section IV); sigma recep-<br>
I ligands (Rao et al., 1990a; Wood and Rao, 1990; N<br>
ction III.B.6.j); and polyamines (Rao et al., 1990c; re<br>
ction III.B.g.i).<br>
In contrast, the actions of harmaline

section III.B.6.j); and polyamines (Rao et al., 1990c; section III.B.g.i).<br>In contrast, the actions of harmaline are not altered<br>by manipulation of cerebellar mossy fiber systems (sec-<br>tion V), including the administration section III.B.6.j); and polyamines (Rao et al., 19<br>section III.B.g.i).<br>In contrast, the actions of harmaline are not alt<br>by manipulation of cerebellar mossy fiber systems (<br>tion V), including the administration of the anti section III.B.g.i).<br>In contrast, the actions of harmaline are not altered<br>by manipulation of cerebellar mossy fiber systems (sec-<br>tion V), including the administration of the anticholin-<br>ergic, atropine (Biggio et al., 197 In contrast, the actions of harmaline are not altered<br>by manipulation of cerebellar mossy fiber systems (sec-<br>tion V), including the administration of the anticholin-<br>ergic, atropine (Biggio et al., 1977c; Opmeer et al., 1 by manipulation of cerebellar mossy fiber systems (sec-<br>tion V), including the administration of the anticholin-<br>pergic, atropine (Biggio et al., 1977c; Opmeer et al., 1976);<br>the antidopaminergic, haloperidol (Biggio et al tion V), including the administration of the anticholinergic, atropine (Biggio et al., 1977c; Opmeer et al., 1976);<br>the antidopaminergic, haloperidol (Biggio et al., 1977c);<br>and by kainate lesions of projection cells in th ergic, atropi<br>the antidops<br>and by kains<br>which inner<br>al., 1978a).<br>The toxin e antidopaminergic, haloperidol (Biggio et al., 1977c);<br>d by kainate lesions of projection cells in the striatum<br>nich innervate pontocerebellar mossy fibers (Biggio et<br>, 1978a).<br>The toxin, 3-acetylpyridine, is an extremely

and by kainate lesions of projection cells in the striatum and<br>which innervate pontocerebellar mossy fibers (Biggio et wer<br>al., 1978a). fect<br>The toxin, 3-acetylpyridine, is an extremely useful tool apse<br>in the study of cer which innervate pontocerebellar mossy fibers (Biggio et were und., 1978a).<br>
fects in the toxin, 3-acetylpyridine, is an extremely useful tool apses.<br>
in the study of cerebellar function in that it induces an action<br>
exten al., 1978a).<br>The toxin, 3-acetylpyridine, is an extremely useful too<br>in the study of cerebellar function in that it induces are<br>**xtensive** lesion of the cerebellar climbing fiber system<br>(reviewed by Balaban, 1985). Several rie with, 3-acetylpyridine, is an extremely useful to<br>in the study of cerebellar function in that it induces a<br>extensive lesion of the cerebellar climbing fiber syste<br>(reviewed by Balaban, 1985). Several aspects of the ne<br>

1989c, 1990a), and is lesioned by the toxin, 3-acetylpyr-<br>igated and indicate that cerebellar aspartate levels are<br>idine (Balaban, 1985; Guidotti et al., 1975). The actions significantly decreased after the lesion occurs, w00D<br>r- tigated and indicate that cerebellar aspartate levels are<br>ns significantly decreased after the lesion occurs, suggesting b<br>tigated and indicate that cerebellar aspartate levels are<br>significantly decreased after the lesion occurs, suggesting<br>that the climbing fiber pathway utilizes an EAA as its<br>neurotransmitter (McBride et al., 1978; Nadi et igated 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 tigated and indicate that cerebellar aspartate levels are<br>significantly decreased after the lesion occurs, suggesting<br>that the climbing fiber pathway utilizes an EAA as its<br>neurotransmitter (McBride et al., 1978; Nadi et a significantly decreased after the lesion occurs, suggesting<br>that the climbing fiber pathway utilizes an EAA as its<br>neurotransmitter (McBride et al., 1978; Nadi et al.,<br>1977). Such lesions remove the incoming climbing fiber that the climbing fiber pathway utilizes an EAA as its<br>neurotransmitter (McBride et al., 1978; Nadi et al.,<br>1977). Such lesions remove the incoming climbing fiber<br>activity which decreases the basal tone of the cerebellar<br>c neurotransmitter (McBride et al., 1978; Nadi et al.<br>1977). Such lesions remove the incoming climbing fibe<br>activity which decreases the basal tone of the cerebella<br>cGMP system(s) by 20 (Mailman et al., 1979) to 40?<br>(Biggio 1977). Such lesions remove the incoming chinomy interactivity 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). Additional (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) withou cGMP system(s) by 20 (Mailman et al., 1979) to 40%<br>(Biggio et al., 1977c,d; Guidotti et al., 1975). Additionally,<br>these lesions selectively block the actions of harmaline<br>on cerebellar cGMP levels (Biggio et al., 1977c,d; (Biggio et al., 1977c,d; Guidotti et al., 1975). Additions<br>these lesions selectively block the actions of harmal<br>on cerebellar cGMP levels (Biggio et al., 1977c,d; C<br>dotti et al., 1975; Mailman et al., 1979) without alter<br> these lesions selectively block the actions of harmaline<br>on cerebellar cGMP levels (Biggio et al., 1977c,d; Gui-<br>dotti et al., 1975; Mailman et al., 1979) without altering<br>the actions of modulators of climbing fibers or in on cerebellar cGMP levels (Biggio et al., 1977c,d; Guidotti et al., 1975; Mailman et al., 1979) without altering<br>the actions of modulators of climbing fibers or intracer-<br>ebellar pathways. The pharmacological agents not af dotti et al., 1975; Mailman et al., 1979) without altering<br>the actions of modulators of climbing fibers or intracer-<br>ebellar pathways. The pharmacological agents not af-<br>fected by 3-acetylpyridine lesions are discussed in the actions of modulators of childing fibers of intracer-<br>ebellar pathways. The pharmacological agents not af-<br>fected by 3-acetylpyridine lesions are discussed in more<br>detail throughout this review, but briefly summarized<br> fected by 3-acetylpyridine lesions are discussed in mordetail throughout this review, but briefly summarized<br>they include (table 5) apomorphine (Biggio et al., 1977c)<br>TRH (Mailman et al., 1979), isoniazid (Biggio et al.<br>19 detail throughout this review, but briefly summarized<br>they include (table 5) apomorphine (Biggio et al., 1977c),<br>TRH (Mailman et al., 1979), isoniazid (Biggio et al.,<br>1977c), haloperidol (Biggio et al., 1977d), diazepam (B TRH (Mailman et al., 1979), i<br>1977c), haloperidol (Biggio et al.,<br>gio et al., 1977d), muscimol (Big<br>morphine (Biggio et al., 1977d). ridol (Biggio et al., 1977d), dia<br>d), muscimol (Biggio et al., 1<br>gio et al., 1977d).<br>V. Mossy Fiber Systems morphine (Biggio et al., 1977d).<br> **V. Mossy Fiber Systems**<br> *A. Anatomy/Neurochemistry* 

V. Mossy Fiber Systems<br>Anatomy/Neurochemistry<br>The mossy fiber pathways are afferent innervations<br>at synapse almost exclusively on cerebellar granule V. Mossy Fiber Systems<br>A. Anatomy/Neurochemistry<br>The mossy fiber pathways are afferent innervations<br>that synapse almost exclusively on cerebellar granule<br>cells. These inputs consist of the spinocerebellar, pon-A. Anatomy/Neurochemistry<br>The mossy fiber pathways are afferent innervation<br>that synapse almost exclusively on cerebellar granu<br>cells. These inputs consist of the spinocerebellar, po<br>tocerebellar, and vestibulocerebellar s The mossy fiber pathways are afferent innervations<br>that synapse almost exclusively on cerebellar granule<br>cells. These inputs consist of the spinocerebellar, pon-<br>tocerebellar, and vestibulocerebellar systems (Allen and<br>Tsu The mossy niser pathways are allerent innervations<br>that synapse almost exclusively on cerebellar granule<br>cells. These inputs consist of the spinocerebellar, pon-<br>tocerebellar, and vestibulocerebellar systems (Allen and<br>Tsu that synapse annost exclusively on cerebenar granue<br>cells. These inputs consist of the spinocerebellar, pon-<br>tocerebellar, and vestibulocerebellar systems (Allen and<br>Tsukahara, 1974); unfortunately, our knowledge base of<br>t tocerebellar, and vestibulocerebellar systems (Allen and Tsukahara, 1974); unfortunately, our knowledge base of the neurochemistry of these pathways is nonexistent.<br>However, we do have some data regarding the chemical make Tsukahara, 1974); unfortunately, our knowledge base the neurochemistry of these pathways is nonexisten<br>However, we do have some data regarding the chemics<br>makeup and pharmacology of a striatal system whicl<br>via a multisynap the neurochemistry of these pathways is honexist.<br>However, we do have some data regarding the chem<br>makeup and pharmacology of a striatal system wh<br>via a multisynaptic pathway (fig. 4), modulates the ac<br>ity of pontocerebell makeup and pharmacology<br> **B. Pharmacology**<br> **B. Pharmacology**<br> **B. Dopaminersic** via a multisynaptic pathway (fig. 4), modulates the activity of pontocerebellar neurons (Biggio et al., 1978a).<br> *B. Pharmacology*<br> *1. Dopaminergic modulators.* A number of early studies<br>
demonstrated that the dopamine ag

ity of pontocerebellar neurons (Biggio et al., 1978a).<br>
B. Pharmacology<br>
1. Dopaminergic modulators. A number of early studies<br>
demonstrated that the dopamine agonist, apomorphine<br>
(Biggio et al., 1977c; Breese et al., 197 B. Pharmacology<br>1. Dopaminergic modulators. A number of early studies<br>demonstrated that the dopamine agonist, apomorphine<br>(Biggio et al., 1977c; Breese et al., 1978; 1979a; Burkard<br>et al., 1976; Gumulka et al., 1976; Mohle **Etheral all alterations:** A number of early studies<br>
demonstrated that the dopamine agonist, apomorphine<br>
(Biggio et al., 1977c; Breese et al., 1978; 1979a; Burkard<br>
et al., 1976; Gumulka et al., 1976; Mohler et al., 1981 1. Dopaminergic modulators. A number of early studies<br>demonstrated that the dopamine agonist, apomorphine<br>(Biggio et al., 1977c; Breese et al., 1978; 1979a; Burkard<br>et al., 1976; Gumulka et al., 1976; Mohler et al., 1981;<br> demonstrated that the dopamine agonist, apomorph<br>(Biggio et al., 1977c; Breese et al., 1978; 1979a; Burk:<br>et al., 1976; Gumulka et al., 1976; Mohler et al., 19<br>Narumi et al., 1983; Puri et al., 1978), the dopam<br>releasers a (Biggio et al., 1977c; Breese et al., 1978; 1979a; Burkard<br>et al., 1976; Gumulka et al., 1976; Mohler et al., 1981;<br>Narumi et al., 1983; Puri et al., 1978), the dopamine<br>releasers amphetamine, methamphetamine and methyl-<br>p et al., 1976; Gumuka et al., 1976; Monier et al., 1981;<br>Narumi et al., 1983; Puri et al., 1978), the dopamine<br>releasers amphetamine, methamphetamine and methyl-<br>phenidate (Breese et al., 1978, 1979a; Gumulka et al.,<br>1976; releasers amphetamine, methamphetamine and methyl-<br>phenidate (Breese et al., 1978, 1979a; Gumulka et al.,<br>1976; Narumi et al., 1983; Wood et al., 1988b), and the<br>dopamine precursor, L-DOPA, in combination with a<br>peripheral phenidate (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), 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 in dopamine precursor, L-DOPA, in combination with a<br>peripheral decarboxylase inhibitor (Gumulka et al.,<br>1976), all increased cerebellar cGMP levels. Studies in<br>which intrastriatal injections of apomorphine (Biggio<br>and Guidot 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 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 effec which intrastriatal injections of apomorphine (Biggio and Guidotti, 1976) and dopamine (Lautie et al., 1981)<br>were used clearly indicated that these dopaminergic ef-<br>fects involved striatal dopaminergic receptors and syn-<br>a and Guidotti, 1976) and dopamine (Lautie et al., 1981)<br>were used clearly indicated that these dopaminergic ef-<br>fects involved striatal dopaminergic receptors and syn-<br>apses. The role of central dopamine receptors in these<br> 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 fects involved striatal dopaminergic receptors and syn-<br>apses. The role of central dopamine receptors in these<br>actions was also supported by antagonism of the actions<br>of apomorphine by a number of brain bioavailable do-<br>pa apses. 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 recept

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input(s) to the cerebellum, which are modulated by striatal dopami-

nergic synapses. DA, dopamine; ACh, acetylcholine.<br>1979a). The importance of the striatum in these drug FIG. 4. Proposed polysynaptic circuitry included in the mossy fiber<br>input(s) to the cerebellum, which are modulated by striatal dopami-<br>nergic synapses. DA, dopamine; ACh, acetylcholine.<br>1979a). The importance of the stri mput(s) to the cerebentum, which are modulated by striature dopaminer<br>nergic synapses. DA, dopamine; ACh, acetylcholine.<br>1979a). The importance of the striatum in these drug<br>effects was further validated using kainate les and the symplect. Err, explanate, rich, acceptance.<br>
1979a). The importance of the striatum in these drug all<br>
effects was further validated using kainate lesions of the<br>
striatum (Biggio et al., 1978a). In this case, the 1979a). The importance of the striatum in these drug aleffects was further validated using kainate lesions of the striatum (Biggio et al., 1978a). In this case, the effects of apomorphine in increasing cerebellar cGMP wer effects was further validated using kainate lesions of the striatum (Biggio et al., 1978a). In this case, the effects of appomorphine in increasing cerebellar cGMP were blocked by such striatal lesions, whereas the effect striatum (Biggio et al., 1978a). In this case, the effects of<br>apomorphine in increasing cerebellar cGMP were<br>blocked by such striatal lesions, whereas the effects of<br>harmaline and isoniazid were unaltered. In addition, it apomorphine in increasing cerebellar cGMP were (left blocked by such striatal lesions, whereas the effects of striarmaline and isoniazid were unaltered. In addition, it is noteworthy that the kainate lesions of the striat blocked by such striatal lesions, whereas the effects of<br>harmaline and isoniazid were unaltered. In addition, it<br>is noteworthy that the kainate lesions of the striatum<br>resulted in time-dependent decreases (6 h = 85% of<br>co harmaline and isoniazid were unaltered. In addition, is<br>is noteworthy that the kainate lesions of the striatun<br>resulted in time-dependent decreases (6 h = 85% o<br>control, 12 h = 67%, 24 h = 31%, 72 h = 26%) in th<br>basal lev is noteworthy that the kainate lesions of the striature resulted in time-dependent decreases  $(6 h = 85\% \text{ o control}, 12 h = 67\%, 24 h = 31\%, 72 h = 26\%)$  in the basal levels of cerebellar CGMP with no change in cere bellar guanylate c sulted in time-dependent decreases  $(6 h = 85\%$  of introl,  $12 h = 67\%$ ,  $24 h = 31\%$ ,  $72 h = 26\%$ ) in the sal levels of cerebellar cGMP with no change in cere-<br>llar guanylate cyclase activity (Biggio et al., 1978a).<br>These d control, 12 h = 67%, 24 h = 31%, 72 h = 26%) in the<br>basal levels of cerebellar cGMP with no change in cere-<br>bellar guanylate cyclase activity (Biggio et al., 1978a).<br>These data indicate that tonic mossy fiber input to the

basal levels of cerebellar cGMP with no change in cerebellar guanylate cyclase activity (Biggio et al., 1978a).<br>These data indicate that tonic mossy fiber input to the cerebellum is a major contributor to the basal levels bellar guanylate cyclase activity (Biggio et al., 1978a).<br>
These data indicate that tonic mossy fiber input to the<br>
cerebellum is a major contributor to the basal levels of<br>
cGMP measured in this brain area. These data hav 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 pontoce CGMP measured in this brain area. I nese data have<br>therefore, led to the speculation of the existence of<br>multisynaptic pathway between the striatum and the<br>pontocerebellar mossy fiber system (fig. 4; Biggio et a<br>1978a). Th 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 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 pontocerebellar mossy liber system (iig. 4; Eiggio et al., 1978a). The kainate lesions support a striatal cell population with efferent fibers reaching the pontine regions; Phowever, the number of synapses in such an outpu lation with efferent fibers reaching the pontine regions; <sup>ph</sup><br>however, the number of synapses in such an output<br>system has not been defined. The enhanced cerebellar st<br>GCMP levels measured after activation of this pathway however, the number of synapses in such an output last approximate system has not been defined. The enhanced cerebellar stimulation stimulation, because the increases elicited in rats matcher paralyzed with d-tubocurarine system has not been defined. The enhanced cerebells  $cGMP$  levels measured after activation of this pathway with apomorphine appear to be partially dependent upomotor stimulation, because the increases elicited in raparaly

cGMP IN THE CEREBELLUM 17<br>lated were smaller than those occurring in free-moving<br>rats (Breese et al., 1979a; Lundberg et al., 1979). How-EREBELLUM<br>lated were smaller than those occurring in free-movint<br>rats (Breese et al., 1979a; Lundberg et al., 1979). How<br>ever, there was no direct correlation between locomote **exemption**<br>
lated were smaller than those occurring in free-moving<br>
rats (Breese et al., 1979a; Lundberg et al., 1979). How-<br>
ever, there was no direct correlation between locomotor<br>
activity and cerebellar cGMP (Breese e ed were smaller than those occurring in free-moving<br>ts (Breese et al., 1979a; Lundberg et al., 1979). How-<br>er, there was no direct correlation between locomotor<br>tivity and cerebellar cGMP (Breese et al., 1979a).<br>In contras

FIG. 4. Proposed polysynaptic circuitry included in the mossy fiber<br>
FIG. 4. Proposed polysynaptic circuitry included in the mossy fiber<br>
FIG. 4. Proposed polysynaptic circuitry included in the mossy fiber<br>
FIG. 4. Propose propyl-2H[l]benzopyrano[3,4-b]pyridin-9-ol (Iyengar et<br>1979a). The importance of the striatum in these drug al., 1989). In these studies, all effective postsynaptic<br>effects was further validated using kainate lesions of th rats (Breese et al., 1979a; Lundberg et al., 1979). How-<br>ever, there was no direct correlation between locomotor<br>activity and cerebellar cGMP (Breese et al., 1979a).<br>In contrast to the actions of the dopamine agonists<br>and stereospecifically decrease basal cGMP levels (Biggio and Guidotti, 1977; Biggio et al., 1977c; Breese et al., 1979a). In contrast to the actions of the dopamine agonists<br>and releasers, dopamine antagonists have been shown to<br>stereospecifically decrease basal cGMP levels (Biggio<br>and Guidotti, 1977; Biggio et al., 1977c; Breese et al.,<br>1978 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 stereospeci These decreases in cerebellar cGMP are also stereospecifically reproduced by intrastriatal, but not intracere-<br>bellar, injections of dopamine antagonists (Biggio et al., 1977d; Biggio and Guidoti, 1977; Breese et al., 1979a; 1978, 1979a; Burkard et al., 1976; Corda et al., 1979).<br>These decreases in cerebellar cGMP are also stereospecifically reproduced by intrastriatal, but not intracere-<br>bellar, injections of dopamine antagonists (Biggio et a These decreases in cerebellar cGMP are also stereospecifically reproduced by intrastriatal, but not intracere-<br>bellar, injections of dopamine antagonists (Biggio et al., 1977d; Biggio and Guidoti, 1977; Breese et al., 1979 cifically reproduced by intrastriatal, but not intracere-<br>bellar, injections of dopamine antagonists (Biggio et al.,<br>1977d; Biggio and Guidoti, 1977; Breese et al., 1979a;<br>Corda et al., 1979). The actions of both dopamine bellar, 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 Forta, Eigele and Guidell, 1911, Ereese of all, 1916,<br>Corda et al., 1979). The actions of both dopamine ago-<br>nists and antagonists were not altered in animals with<br>lesions produced by 3-acetylpyridine, indicating a lack of 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 eff ness and analyons as were not anoted in annihas when<br>lesions produced by 3-acetylpyridine, indicating a lack of<br>involvement of climbing fibers in the observed drug<br>effects (Biggio et al., 1977d). Studies (Biggio et al., 19 the producted by a decly-pyridine, indicating a fact of<br>involvement of climbing fibers in the observed drug<br>effects (Biggio et al., 1977d). Studies (Biggio et al., 1978c)<br>of chronic neuroleptic treatment (haloperidol, 0.5 mvolvement of emmong modes in the observed diverted effects (Biggio et al., 1978). Studies (Biggio et al., 1978) of chronic neuroleptic treatment (haloperidol, 0.5 mg/<br>twice daily for 20 days) have shown tolerance to the d ented (Eight ovality, 1977a), Solands (Eight ovality, 1976b)<br>of chronic neuroleptic treatment (haloperidol, 0.5 mg/g,<br>twice daily for 20 days) have shown tolerance to the<br>decreases in cGMP levels induced by haloperidol tre twice daily for 20 days) have shown tolerance to the<br>decreases in cGMP levels induced by haloperidol treat-<br>ment. Additionally, these tolerant rats were shown to<br>express enhanced sensitivity to apomorphine-induced<br>cGMP inc decreases in cGMP levels induced by haloperidol trement. Additionally, these tolerant rats were shown express enhanced sensitivity to apomorphine-induce GMP increases, suggesting that cGMP is a sensitividex of the level of ment. Additionally, these tolerant rats were shown to<br>express enhanced sensitivity to apomorphine-induced<br>cGMP increases, suggesting that cGMP is a sensitive<br>index of the level of striatal dopamine receptor activa-<br>tion (B express emianced sensurity to apomorphine mateca 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 index of the level of striatal dopamine receptor activaition (Biggio et al., 1978b). This contention has been appointed in studies of the presynaptic to postsynap dose-response relationships for the dopamine agon appomorphine, and the more selective dopamine autore-<br>ceptor ago tion (Biggio et al., 1978b). This contention has<br>supported in studies of the presynaptic to postsyn<br>dose-response relationships for the dopamine ag<br>apomorphine, and the more selective dopamine at<br>ceptor agonist, (±)-*trans* dose-response relationships for the dopamine agonist,<br>apomorphine, and the more selective dopamine autore-<br>ceptor agonist,  $(\pm)$ -*trans*-1,3,4,4a,10b-hexahydro-4-<br>propyl-2H[l]benzopyrano[3,4-b]pyridin-9-ol (Iyengar et<br>al., absortationships for the dopamine agonst,<br>apomorphine, and the more selective dopamine autore-<br>ceptor agonist,  $(\pm)$ -trans-1,3,4,4a,10b-hexahydro-4-<br>propyl-2H[l]benzopyrano[3,4-b]pyridin-9-ol (Iyengar et<br>al., 1989). In the al., 1989). In these studies, all effective postsynaptic ceptor agonist,  $(\pm)$ -trans-1,3,4,4a,10b-hexahydro-4-<br>propyl-2H[l]benzopyrano[3,4-b]pyridin-9-ol (Iyengar et<br>al., 1989). In these studies, all effective postsynaptic<br>dopamine receptor doses, as assessed by changes in stri (Iyengar et al., 1989). In these studies, all effective postsynaptic dopamine receptor doses, as assessed by changes in striated acetylcholine levels, also increased cerebellar cGMP (Iyengar et al., 1989), suggesting modul striato-pontocerebellar mossy fiber pathway.<br>In acctylcholine levels, also increased cereb<br>(Iyengar et al., 1989), suggesting modula<br>striato-pontocerebellar mossy fiber pathway.<br>From these studies, it has been suggested From these studies, as assessed by changes in striated acctylcholine levels, also increased cerebellar cGMP vengar et al., 1989), suggesting modulation of the riato-pontocerebellar mossy fiber pathway.<br>From these studies,

cerebellum is a major contributor to the basal levels of<br>cGMP measured in this brain area. These data have,<br>therefore, led to the speculation of the existence of a<br>multisynaptic pathway between the striatum and the<br>pontoc (Iyengar et al., 1989), suggesting modulation of the striato-pontocerebellar mossy fiber pathway.<br>From these studies, it has been suggested that there is a tonic net excitatory effect on pontocerebellar mossy fibers via st fiveligat et al., 1999), suggessing modulation of the<br>striato-pontocerebellar mossy fiber pathway.<br>From these studies, it has been suggested that there is<br>a tonic net excitatory effect on pontocerebellar mossy<br>fibers via s striato-pontocerebellar mossy fiber pathway.<br>From these studies, it has been suggested that there is<br>a tonic net excitatory effect on pontocerebellar mossy<br>fibers via striatal output neurons which can be further<br>potentiate From these studies, it has been suggested that there<br>a tonic net excitatory effect on pontocerebellar mos<br>fibers via striatal output neurons which can be furth<br>potentiated by dopamine agonists or releasers. One pie<br>of dat a tonic net excitatory effect on pontocerebellar most<br>fibers via striatal output neurons which can be furth<br>potentiated by dopamine agonists or releasers. One pie<br>of data inconsistent with this hypothesis is that inhil<br>ti potentiated by dopamine agonists or releasers. One piece of data inconsistent with this hypothesis is that inhibition of dopamine synthesis with  $\alpha$ -methyl-paratyrosine does not alter basal cGMP levels (Narumi et al., 1983). does not alter basal cGMP levels (Narumi et al., 1983<br>Although these negative data clearly require reevaluation, a similar finding has been reported for 6-hydroxy<br>dopamine treatments, which do not alter basal cGM<br>levels ( Atthough these hegative data clearly require reevalu-<br>ation, a similar finding has been reported for 6-hydroxy-<br>dopamine treatments, which do not alter basal CGMP<br>levels (Mao et al., 1974a). The  $\alpha$ -methyl-paratyrosine<br>t depannie creatineires, which do not after basafr contributed<br>levels (Mao et al., 1974a). The  $\alpha$ -methyl-paratyrosine<br>treatments, however, did antagonize the actions of am-<br>phetamine in increasing cerebellar CGMP (Narumi striatal dopamine content was not reported; therefore, a<br>phetamine in increasing cerebellar cGMP (Narumi et al.,<br>1983). In both of these studies, the measurement of<br>striatal dopamine content was not reported; therefore, a<br> phetalline in increasing cerebellar colorical (Natural 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 prese striated topenine content was not reported, therefore, a<br>small functional dopamine pool may have been present<br>and capable of maintaining basal dopaminergic trans-<br>mission and thus not altering cerebellar cGMP. However,<br>res

18<br>norepinephrine, does decrease cerebellar cGMP (Rubin ox<br>and Ferrendelli, 1977). 18<br>norepinephrine, does de<br>and Ferrendelli, 1977).<br>Another possible expl

Frepinephrine, does decrease cerebellar cGMP (Ruld Ferrendelli, 1977).<br>Another possible explanation for some of the discret data, with regard to the tonicity of this dopamin norepinephrine, does decrease cerebellar cGMP (Ru<br>and Ferrendelli, 1977).<br>Another possible explanation for some of the disc<br>ant data, with regard to the tonicity of this dopam<br>modulated output from the striatum, is the obs morepinephrine, does decrease cerebellar cGMP (Rubin<br>and Ferrendelli, 1977).<br>Another possible explanation for some of the discrep-<br>ant data, with regard to the tonicity of this dopamine-<br>modulated output from the striatum, emplement and Ferrendelli, 1977).<br>
Another possible explanation for some of the discrep-<br>
ant data, with regard to the tonicity of this dopamine-<br>
modulated output from the striatum, is the observation<br>
that, in rats habit Another possible explanation for some of the discrepant data, with regard to the tonicity of this dopamine-<br>modulated output from the striatum, is the observation<br>that, in rats habituated to handling, basal cGMP levels<br>are ant data, whil regard to the tomchty of this dopamine-<br>modulated output from the striatum, is the observation p<br>that, in rats habituated to handling, basal CGMP levels n<br>are lower than in naive rats and that dopamine antag that, in rats habituated to handling, basal cGMP levels nare lower than in naive rats and that dopamine antago-<br>nists cannot further decrease the cGMP levels in these canimals (Corda et al., 1980). These data indicate that are lower than in naive rats and that dopamine antago-<br>nists cannot further decrease the cGMP levels in these<br>enimals (Corda et al., 1980). These data indicate that<br>the decreases in basal cerebellar cGMP levels measured<br>af mists cannot further decrease the cGMP levels in these<br>animals (Corda et al., 1980). These data indicate that<br>the decreases in basal cerebellar cGMP levels measured<br>after dopamine antagonist treatments may well depend<br>upon animals (Corda et al., 1980). These data indicate that muss<br>the decreases in basal cerebellar cGMP levels measured T<br>after dopamine antagonist treatments may well depend and<br>upon the degree of stress elevation of basal cGM the decreases in basal cerebellar cGMP levels measured<br>after dopamine antagonist treatments may well depend<br>upon the degree of stress elevation of basal cGMP levels,<br>a notion consistent with dopaminergic involvement in<br>str after dopamine antagonist trupon the degree of stress elev.<br>a notion consistent with dop<br>stress-induced cGMP increa<br>mulka, 1977; section II.E.2).<br>The actions of apomorphir on the degree of stress elevation of basal cGMP levels, in c<br>notion consistent with dopaminergic involvement in 3.<br>ress-induced cGMP increases (Dinnendahl and Gu-<br>ulka, 1977; section II.E.2).<br>The actions of apomorphine hav

a notion consistent with dopaminergic involvement stress-induced cGMP increases (Dinnendahl and mulka, 1977; section II.E.2).<br>The actions of apomorphine have also been show be blocked by pretreatment with the central antic stress-induced cGMP increases (Dinnendahl and Gumulka, 1977; section II.E.2).<br>
The actions of apomorphine have also been shown to<br>
be blocked by pretreatment with the central anticholin-<br>
ergics, trihxyphenidyl (Biggio et mulka, 1977; section II.E.2). dy<br>The actions of apomorphine have also been shown to<br>be blocked by pretreatment with the central anticholin-<br>cergics, trihxyphenidyl (Biggio et al., 1977c) and hyoscine<br>National (Burkard et a Ine actions of apomorphine have also been shown to<br>be blocked by pretreatment with the central anticholin-<br>ergics, trihxyphenidyl (Biggio et al., 1977c) and hyoscine<br>(Burkard et al., 1976), but not by methylatropine, which ergics, trihxyphenidyl (Biggio et al., 1977c) and hyosci<br>(Burkard et al., 1976), but not by methylatropine, whis<br>is not brain bioavailable, indicating a central action<br>the anticholinergics in blocking apomorphine (Burka<br>et (Burkard et al., 1976), but not by methylatropine, which rise not brain bioavailable, indicating a central action of perfection the anticholinergics in blocking apomorphine (Burkard 7 et al., 1976). These data indicate tha is not brain bioavailable, indicating a central action of the anticholinergics in blocking apomorphine (Burkaret al., 1976). These data indicate that there is a cholinergic synapse downstream to the dopaminergic synaps in the anticholinergics in blocking apomorphine (Burkard<br>et al., 1976). These data indicate that there is a cholin-<br>ergic synapse downstream to the dopaminergic synapse<br>in this multisynaptic pathway to the pontocerebellar<br>mos ergic synapse downstream to the dopaminergic synapse of a<br>in this multisynaptic pathway to the pontocerebellar have<br>mossy fiber system. The exact location of the cholinergic sys<br>synapse involved is currently unknown but i ergic synapse downstream to the dopaminergic synapse<br>in this multisynaptic pathway to the pontocerebellar<br>mossy fiber system. The exact location of the cholinergic<br>synapse involved is currently unknown but is unlikely to<br>b

mossy fiber system. The exact location of the cholinergic<br>synapse involved is currently unknown but is unlikely to<br>be within the striatum (Burkard et al., 1976).<br>2. *Cholinergic modulators*. The muscarinic agonists<br>oxotrem synapse involved is currently unknown but is unlikely to<br>be within the striatum (Burkard et al., 1976).<br>2. Cholinergic modulators. The muscarinic agonists<br>oxotremorine, pilocarpine, and arecoline (Dinnendahl<br>and Stock, 197 be within the striatum (Burkard et al., 1976).<br>
2. Cholinergic modulators. The muscarinic agonists<br>
oxotremorine, pilocarpine, and arecoline (Dinnendahl<br>
and Stock, 1975; Dodson and Johnson, 1979; Ferrendelli<br>
et al., 1970 2. Cholinergic modulators. The muscarinic agonists noxotremorine, pilocarpine, and arecoline (Dinnendahl A<br>and Stock, 1975; Dodson and Johnson, 1979; Ferrendelli ret al., 1970; Gumulka et al., 1976; Opmeer et al., 1976; f<br> oxotremorine, pilocarpine, and arecoline (Dinnendal<br>and Stock, 1975; Dodson and Johnson, 1979; Ferrende<br>et al., 1970; Gumulka et al., 1976; Opmeer et al., 197<br>Puri et al., 1978; Rubin and Ferrendelli, 1977; Wood<br>al., 1982) and Stock, 1970; Douson and Johnson, 1979, Ferrendent<br>et al., 1970; Gumulka et al., 1976; Opmeer et al., 1976; fi<br>Puri et al., 1978; Rubin and Ferrendelli, 1977; Wood et<br>al., 1982) as well as the nicotinic agonist, nicotin et al., 1970; Gumulka et al., 1976; Opmeer et al., 19<br>Puri et al., 1978; Rubin and Ferrendelli, 1977; Wood<br>al., 1982) as well as the nicotinic agonist, nicotine (D<br>son and Johnson, 1979), all dose dependently and t<br>depende 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. Interesti al., 1982) as well as the nicotinic agonist, nicotine (Dowson and Johnson, 1979), all dose dependently and tin<br>dependently increase cerebellar CGMP levels. Interes<br>ingly, the increases in CGMP elicited by oxotremorin<br>were son and Johnson, 1979), all dose dependently and time<br>dependently increase cerebellar cGMP levels. Interest-<br>ingly, the increases in cGMP elicited by oxotremorine<br>were only monitored in the vermis but not the hemi-<br>spheres dependently increase cerebellar cGMP levels. Interest-<br>ingly, the increases in cGMP elicited by oxotremorine lar<br>were only monitored in the vermis but not the hemi-<br>effects can be spheres of the cerebellum (Rubin and Ferre ingly, the increases in cGMP elicited by oxotremorine lumes 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 b were only monitored in the vermis but not the hem<br>spheres of the cerebellum (Rubin and Ferrendelli, 1977<br>These data suggest that more topographic effects can h<br>observed with cerebellar cGMP changes after mossy fibe<br>activat spheres of the cerebellum (These data suggest that m<br>observed with cerebellar cC<br>activation than is evident<br>cerebellar circuit changes.<br>In contrast, cholinesters nese data suggest that more topographic effects can be<br>served with cerebellar cGMP changes after mossy fibe<br>tivation than is evident with climbing fiber or intra<br>rebellar circuit changes.<br>In contrast, cholinesterase inhibi

observed with cerebellar cGMP changes after mossy fiber<br>activation than is evident with climbing fiber or intra-<br>cerebellar circuit changes.<br>In contrast, cholinesterase inhibitors exert more com-<br>plex effects, in that earl activation than is evident with climbing fiber or interrebellar circuit changes.<br>In contrast, cholinesterase inhibitors exert more coplex effects, in that early (10 min) increases in cerebe<br>cGMP are followed by decreases a cerebellar circuit changes. the incontrast, cholinesterase inhibitors exert more com-<br>plex effects, in that early (10 min) increases in cerebellar E<br>cGMP are followed by decreases at 30–60 min (Dinnen-<br>dahl and Stock, 1975 In contrast, cholinesterase inhibitors exert more com-<br>plex effects, in that early (10 min) increases in cerebellar<br>cGMP are followed by decreases at 30–60 min (Dinnen-<br>dahl and Stock, 1975). These effects may well involve cGMP are followed by decreases at 30–60 min (Dinnen-<br>dahl and Stock, 1975). These effects may well involve<br>later multisynaptic effects of cholinesterase inhibition<br>but require more in-depth studies.<br>Antimuscarinics do not

dahl and Stock, 1975). These effects may well involve<br>later multisynaptic effects of cholinesterase inhibition<br>but require more in-depth studies. m<br>Antimuscarinics do not alter cerebellar basal cGMP<br>mevels (Biggio et al., later multisynaptic effects of cholinesterase inhibition<br>but require more in-depth studies.<br>Antimuscarinics do not alter cerebellar basal cGMP<br>levels (Biggio et al., 1977c,d; Burkard et al., 1976; Costa<br>et al., 1974; Dodso out require more m-depth statutes.<br>
Antimuscarinics do not alter cerebellar basal cGMP<br>
levels (Biggio et al., 1977c,d; Burkard et al., 1976; Costa<br>
et al., 1974; Dodson and Johnson, 1979; Mailman et al.,<br>
1979; Mao et al. Antimuscarinics do not alter cerebellar basal cGMP<br>levels (Biggio et al., 1977c,d; Burkard et al., 1976; Costa<br>et al., 1974; Dodson and Johnson, 1979; Mailman et al.,<br>1979; Mao et al., 1974a), except at extremely high dose levels (Biggio et al., 1977c,d; Burkard et al., 1976; Costa si<br>et al., 1974; Dodson and Johnson, 1979; Mailman et al., a<br>1979; Mao et al., 1974a), except at extremely high doses el<br>(Ferrendelli et al., 1970; Rubin and Ferr 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).<br>However, at effective antimuscarinic doses, atropine 1979; Mao et al., 1974a), except at extremely high doses (Ferrendelli et al., 1970; Rubin and Ferrendelli, 1977).<br>However, at effective antimuscarinic doses, atropine or trihexyphenidyl has been shown to block the increase

oxotremorine, (Dinnendahl and Stock, 1975; Ferrendelli<br>et al., 1970; Opmeer et al., 1976) and the dopamine et al., 1970; Opmeer et al., 1976, 1975; Ferrendelli<br>et al., 1970; Opmeer et al., 1976) and the dopamine<br>agonist, apomorphine (Biggio et al., 1977c; Burkard et<br>al., 1976). In contrast, the antimuscarinic, methylatrooxotremorine, (Dinnendahl and Stock, 1975; Ferren<br>et al., 1970; Opmeer et al., 1976) and the dopar<br>agonist, apomorphine (Biggio et al., 1977c; Burkar<br>al., 1976). In contrast, the antimuscarinic, methyla<br>pine, which does no oxotremorine, (Dinnendahl and Stock, 1975; Ferrendelli<br>et al., 1970; Opmeer et al., 1976) and the dopamine<br>agonist, apomorphine (Biggio et al., 1977c; Burkard et<br>al., 1976). In contrast, the antimuscarinic, methylatro-<br>pin 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 agonist, apomorphine (Biggio et al., 1977c; Burkard et al., 1976). In contrast, the antimuscarinic, methylatro-<br>pine, which does not cross the blood-brain barrier, does<br>not block the effects of oxotremorine (Opmeer et al., al., 1976). In contrast, the antimuscarinic, methylatro-<br>pine, which does not cross the blood-brain barrier, does<br>not block the effects of oxotremorine (Opmeer et al.,<br>1976) or apomorphine (Burkard et al., 1976) to increas pine, which does not cross the blood-brain barrier, does<br>not block the effects of oxotremorine (Opmeer et al.,<br>1976) or apomorphine (Burkard et al., 1976) to increase<br>cerebellar cGMP, clearly indicating that the effects of t block the effects of oxotremorine (Opmeer et al., 76) or apomorphine (Burkard et al., 1976) to increase rebellar cGMP, clearly indicating that the effects of uscarinic agonists are centrally mediated.<br>The ganglionic (nic

cerebellar cGMP, clearly indicating that the effects of muscarinic agonists are centrally mediated.<br>The ganglionic (nicotinic) blockers, mecamylamine<br>and chlorisondamine, do not alter cerebellar cGMP levels<br>in control or c in control or cold-stressed rats (Mao et al., 1974a).<br> **3. The ganglionic (nicotinic)** blockers, mecamylamine<br>
and chlorisondamine, do not alter cerebellar cGMP levels<br>
in control or cold-stressed rats (Mao et al., 1974a).

The ganglionic (nicotinic) blockers, mecaning and chlorisondamine, do not alter cerebellar cGM in control or cold-stressed rats (Mao et al., 1974 3. Thyrotropin-releasing hormone analogues. The TRH analogues, DN-1417, L-py and chlorisondamine, do not alter cerebellar cGMF<br>in control or cold-stressed rats (Mao et al., 1974a)<br>3. Thyrotropin-releasing hormone analogues. TR<br>the TRH analogues, DN-1417, L-pyroglutamyl-I<br>dyl-3,3-dimethyl proline am in control or cold-stressed rats (Mao et al., 1974a).<br>3. Thyrotropin-releasing hormone analogues. TRH and<br>the TRH analogues, DN-1417, L-pyroglutamyl-L-histi-<br>dyl-3,3-dimethyl proline amide, and L-pyro-2-aminodi-<br>pyl-L-hist 3. Thyrotropin-releasing hormone analogues. TRH and<br>the TRH analogues, DN-1417, L-pyroglutamyl-L-histi-<br>dyl-3,3-dimethyl proline amide, and L-pyro-2-aminodi-<br>pyl-L-histidyl-L-thiazolidine-4-carboxamide, all increase<br>cerebe dyl-3,3-dimethyl proline amide, and L-pyro-2-aminodi-<br>dyl-3,3-dimethyl proline amide, and L-pyro-2-aminodi-<br>pyl-L-histidyl-L-thiazolidine-4-carboxamide, all increase<br>cerebellar CGMP in rats and mice (Mailman et al., 1979;<br> dy1-0,0-dimetry1 prome annue, and L-py10-2-annifodal<br>pyl-L-histidyl-L-thiazolidine-4-carboxamide, all increase<br>cerebellar cGMP in rats and mice (Mailman et al., 1973)<br>Narumi et al., 1983; Rinehart et al., 1986). The exade<br> pyl-L-histidyl-L-thiazolidine-4-carboxamide, all increase<br>cerebellar cGMP in rats and mice (Mailman et al., 1979;<br>Narumi et al., 1983; Rinehart et al., 1986). The exact<br>mechanism of action remains undefined for these com-<br> cerebellar cGMP in rats and mice (Mailman et al., 1979;<br>Narumi et al., 1983; Rinehart et al., 1986). The exact<br>mechanism of action remains undefined for these com-<br>pounds; however, experiments with central injections of<br>TR Narumi et al., 1983; Rinehart et al., 1986). The exact<br>mechanism of action remains undefined for these com-<br>pounds; however, experiments with central injections of<br>TRH and measurement of TRH levels in the CNS after<br>periphe mechanism of action remains underlied for these com-<br>pounds; however, experiments with central injections of<br>TRH and measurement of TRH levels in the CNS after<br>peripheral administration argue in favor of a CNS locus<br>of act peripheral administration argue in favor of a CNS locus<br>of action. Studies of lesions produced by 3-acetylpyridine<br>have ruled out a modulatory effect on the climbing fiber<br>system (Mailman et al., 1979).<br>A number of studies of action. Studies of lesions produced by 3-acetylpyridine

of action. Studies of lesions produced by 3-acetylpyridine<br>have ruled out a modulatory effect on the climbing fiber<br>system (Mailman et al., 1979).<br>A number of studies have demonstrated the ability of<br>TRH analogues to relea nave ruleu out a modulatory effect on the chimolog inser<br>system (Mailman et al., 1979).<br>A number of studies have demonstrated the ability of<br>TRH analogues to release dopamine in the striatum and<br>nucleus acuumbens (Narumi e 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, therefor TRH analogues to release dopamine in the striatum incleus acuumbens (Narumi et al., 1983; Wood a<br>Altar, 1988). Such data suggest that TRH analog<br>might, therefore, modulate cerebellar cGMP via a mortiber pathway. Experimen Altar, 1988). Such data suggest that TRH analogue<br>might, therefore, modulate cerebellar cGMP via a moss,<br>fiber pathway. Experiments with the tyrosine hydroxyl<br>ase inhibitor,  $\alpha$ -methyl-paratyrosine, support this con-<br>clu Altar, 1988). Such data suggest that TRH analogues<br>might, therefore, modulate cerebellar cGMP via a mossy<br>fiber pathway. Experiments with the tyrosine hydroxyl-<br>ase inhibitor,  $\alpha$ -methyl-paratyrosine, support this con-<br>c might, therefore, modulate cerebellar cGMP via a if<br>fiber pathway. Experiments with the tyrosine hyd<br>ase inhibitor,  $\alpha$ -methyl-paratyrosine, support this<br>clusion in that such treatments block the effects of<br>DN-1417, and fiber pathway. Experiments with the tyrosine hydroxy<br>ase inhibitor,  $\alpha$ -methyl-paratyrosine, support this conclusion in that such treatments block the effects of TRI<br>DN-1417, and the dopamine releaser, methamphetamine, o ase inhibitor,  $\alpha$ -methyl-paratyrosine, support this conclusion in that such treatments block the effects of TRH,<br>DN-1417, and the dopamine releaser, methampheta-<br>mine, on cerebellar cGMP (Narumi et al., 1983). Simi-<br>lar clusion in that such treatments block the effects of TRH<br>DN-1417, and the dopamine releaser, methampheta<br>mine, on cerebellar cGMP (Narumi et al., 1983). Simi<br>larly, the D-2 receptor antagonist, pimozide, blocks the<br>effect DN-1417, and the dopamine releaser, methampheta-<br>mine, on cerebellar cGMP (Narumi et al., 1983). Simi-<br>larly, the D-2 receptor antagonist, pimozide, blocks the<br>effect of DN-1417, apomorphine, and methamphetamine<br>(Narumi et mine, on cerebellar cGMP (Narumi et al., 1983). Simi-<br>larly, the D-2 receptor antagonist, pimozide, blocks the<br>effect of DN-1417, apomorphine, and methamphetamine<br>(Narumi et al., 1983). However, D-2 receptor blockade<br>with larly, the D-2 receptor antagonist, pimozide, blocks the<br>effect of DN-1417, apomorphine, and methamphetamine<br>(Narumi et al., 1983). However, D-2 receptor blockade<br>with either pimozide (Narumi et al., 1983) or haloperidol<br>( 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. (Narumi et al., 1983). However, D-2 receptor blockade<br>with either pimozide (Narumi et al., 1983) or haloperidol<br>(Mailman et al., 1979) does not block the actions of<br>TRH. These apparently contradictory data require fur-<br>the (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. (Mailman et al., 1979) does not block the actions of TRH. These apparently contradictory data require fur-<br>ther evaluation, but a modulatory effect of these ana-<br>logues on mossy fiber systems is suggested at this time.<br>Dir TRH. These apparently contradict<br>ther evaluation, but a modulatory<br>logues on mossy fiber systems is sup<br>Direct effects of TRH on guanylat<br>discounted (Mailman et al., 1979).<br>In studies in which artificially vent

CGMP are followed by decreases at 30–60 min (Dinnen-<br>discounted (Mailman et al., 1979).<br>dahl and Stock, 1975). These effects may well involve In studies in which artificially ventilated rats paralyzed<br>later multisynaptic In studies in which artificially ventilated rats paralyzed logues on mossy fiber systems is suggested at this time.<br>Direct effects of TRH on guanylate cyclase have been<br>discounted (Mailman et al., 1979).<br>In studies in which artificially ventilated rats paralyzed<br>with d-tubocurarin Direct enects of  $2$  KH on guanyiate cyclose have been<br>discounted (Mailman et al., 1979).<br>In studies in which artificially ventilated rats paralyzee<br>with  $d$ -tubocurarine, as compared to free-moving ani<br>mals, were used, i In studies in which artificially ventilated rats paralyzed<br>with d-tubocurarine, as compared to free-moving ani-<br>mals, were used, it appears that, as observed with apo-<br>morphine, the effects of TRH on cerebellar cGMP are<br>si with *d*-tubocurarine, as compared to free-moving ani-<br>mals, were used, it appears that, as observed with apo-<br>morphine, the effects of TRH on cerebellar cGMP are<br>significantly reduced, indicating that increased motor<br>act mals, were used, it appears that, as observed<br>morphine, the effects of TRH on cerebellar c<br>significantly reduced, indicating that increas<br>activity contributes to the elevated cyclic nucle<br>les after this peptide (Lundberg e significantly reduced, indicating that increased motor activity contributes to the elevated cyclic nucleotide lev-<br>els after this peptide (Lundberg et al., 1979).<br>4. Cholecystokinin receptor modulators. There are cur-

rently two major CCK receptor subtypes. The CCK-A, or peripheral type, CCK receptor has high affinity only activity contributes to the elevated cyclic nucleotide lev-<br>els after this peptide (Lundberg et al., 1979).<br>4. Cholecystokinin receptor modulators. There are cur-<br>rently two major CCK receptor subtypes. The CCK-A,<br>or perip els after this peptide (Lundberg et al., 1979).<br>4. Cholecystokinin receptor modulators. There are currently two major CCK receptor subtypes. The CCK-A,<br>or peripheral type, CCK receptor has high affinity only<br>for the sulfat

cGMP IN THE<br>or more (reviewed by Wood et al., 1988b); this receptor<br>subtype is also present in the brain. Proglumide and CRcGMP IN THE or more (reviewed by Wood et al., 1988b); this receptor<br>subtype is also present in the brain. Proglumide and CR-<br>1409 are antagonists of this receptor subtype. The CCK-CGMP IN T<br>1409 are antagonists of this receptor subtype is also present in the brain. Proglumide and CI<br>1409 are antagonists of this receptor subtype. The CCI<br>1409 are antagonists of this receptor subtype. The CCI<br>1409 are or more (reviewed by Wood et al., 1988b); this receptor acts subtype is also present in the brain. Proglumide and CR-<br>1409 are antagonists of this receptor subtype. The CCK-<br>B, or brain, receptor is less discriminatory in or more (reviewed by Wood et al., 1988b); this receptor acts aboutly pe is also present in the brain. Proglumide and CR-<br>1409 are antagonists of this receptor subtype. The CCK-<br>19 B, or brain, receptor is less discriminato subtype is also present in the brain. Proglumide and CR-1409 are antagonists of this receptor subtype. The CCK-<br>B, or brain, receptor is less discriminatory in that it also<br>has high affinity for CCK-4 and unsulfated forms 1989). or brain, receptor is less discriminatory in that it also not as high affinity for CCK-4 and unsulfated forms of the deger peptide fragments (Wood et al., 1988b; Wood, N<br>89).<br>Initial observations that parenteral administra

has high affinity for CCK-4 and unsulfated forms of the larger peptide fragments (Wood et al., 1988b; Wood, 1989).<br>
Initial observations that parenteral administration of CCK would antagonize the tremorogenic effects of ha Initial observations that parenteral administration of tremely high doses (60–240 mg/kg) this drug elicited CCK would antagonize the tremorogenic effects of har-<br>CCK would antagonize the tremorogenic effects of har-<br>maline 1989).<br>
Initial observations that parenteral administration of<br>
CCK would antagonize the tremorogenic effects of har-<br>
maline (Zettler, 1983) led to the evaluation of CCK<br>
analogues on cerebellar cGMP levels (Wood et al.,<br> Initial observations that parenteral administration of track-CCK would antagonize the tremorogenic effects of hardomaline (Zettler, 1983) led to the evaluation of CCK G.<br>analogues on cerebellar cGMP levels (Wood et al., 19 CCK would antagonize the tremorogenic effects of har-<br>maline (Zettler, 1983) led to the evaluation of CCK GA<br>analogues on cerebellar CGMP levels (Wood et al., 5<br>1988b). CCK-8 sulfate, CCK-8 unsulfated, and CCK-4 pyr<br>all do maline (Zettler, 1983) led to the evaluation of CCK<br>analogues on cerebellar cGMP levels (Wood et al.,<br>1988b). CCK-8 sulfate, CCK-8 unsulfated, and CCK-4<br>all dose dependently decreased basal cerebellar cGMP<br>levels, suggesti 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 conclus 1988b). CCK-8 sulfate, CCK-8 unsulfated, and CCK-4 pyintide or CR 1804 to all dose dependently decreased basal cerebellar cGMP 197 levels, suggesting activity at the CCK-B type receptor. injurially of pro-<br>This conclusion all dose dependently decreased basal cerebellar cGMP 1<br>levels, suggesting activity at the CCK-B type receptor. if<br>This conclusion was supported by the inability of pro-<br>glumide or CR 1409 to antagonize the effects on cGMP levels, suggesting activity at the CCK-B type receptor. injecti<br>This conclusion was supported by the inability of pro-<br>glumide or CR 1409 to antagonize the effects on cGMP data a<br>levels. No opioid involvement was suggested This conclusion was supported by the inability of pro-<br>glumide or CR 1409 to antagonize the effects on cGMP<br>levels. No opioid involvement was suggested, because<br>naloxone pretreatment did not modify the effects of CCK<br>(Wood umide or CR 1409 to antagonize the effects on cGMP<br>vels. No opioid involvement was suggested, because<br>loxone pretreatment did not modify the effects of CCK<br>Vood et al., 1988b).<br>The effects of CCK-8 sulfate on cGMP levels,

levels. No opioid involvement was suggested, because<br>naloxone pretreatment did not modify the effects of CCK<br>(Wood et al., 1988b).<br>The effects of CCK-8 sulfate on cGMP levels, aug-<br>mented by various stimulants, were also i maloxone pretreatment did not modify the effects of CCK mo<br>
(Wood et al., 1988b). bel<br>
The effects of CCK-8 sulfate on cGMP levels, aug-<br>
sup<br>
mented by various stimulants, were also investigated dep<br>
(Wood et al., 1988b; (Wood et al., 1988b).<br>The effects of CCK-8 sulfate on cGMP levels, a<br>mented by various stimulants, were also investiga<br>(Wood et al., 1988b; Wood, 1989). Pretreatments w<br>CCK were found to antagonize the effects of dopan<br>ner The effects of CCK-8 sulfate on cGMP levels, aug-<br>mented by various stimulants, were also investigated<br>(Wood et al., 1988b; Wood, 1989). Pretreatments with<br>CCK were found to antagonize the effects of dopami-<br>nergic (amphet (Wood et al., 1988b; Wood, 1989). Pretreatments w<br>CCK were found to antagonize the effects of dopan<br>nergic (amphetamine, apomorphine, DN-1417) and cl<br>linergic (oxotremorine) mossy fiber stimulation, as w<br>as climbing fiber CCK were found to antagonize the effects of dopami-<br>nergic (amphetamine, apomorphine,  $DN-1417$ ) and cho-<br>linergic (oxotremorine) mossy fiber stimulation, as well nal<br>as climbing fiber activation by harmaline. This modulaas climbing fiber activation by harmaline. This modula-<br>tion was not a local cerebellar effect as reflected by lack<br>of activity after direct intracerebellar injections of CCK<br>on cerebellar cGMP have been reported, with inc linergic (oxotremorine) mossy fiber stimulation, as we<br>as climbing fiber activation by harmaline. This modul<br>tion was not a local cerebellar effect as reflected by la<br>of activity after direct intracerebellar injections of as climbing fiber activation by harmaline. This modulation was not a local cerebellar effect as reflected by lack<br>of activity after direct intracerebellar injections of CCK<br>(201). These data, therefore, argue in favor of a tion was not a local cerebellar effect as reflected by lack<br>of activity after direct intracerebellar injections of CCK<br>(201). These data, therefore, argue in favor of an extra-<br>incerebellar modulation of both climbing and of activity after direct intracerebellar injections of CCK on<br>(201). These data, therefore, argue in favor of an extra-<br>incerebellar modulation of both climbing and mossy fiber<br>linput to the cerebellum by CCK. In support o (201). These data, therefore, argue in favor of an extr. cerebellar modulation of both climbing and mossy fibling input to the cerebellum by CCK. In support of the hypothesis, CCK was found not to alter the effects of the toxin. put to the cerebellum by CCK. In support of this encepthesis, CCK was found not to alter the effects of the motracerebellar convulsants, pentylenetetrazol and picro-<br>xin. 1986<br>Caerulein, a peptide chemically related to CCK hypothesis, CCK was found not to alter the effects intracerebellar convulsants, pentylenetetrazol and proxim.<br>
Caerulein, a peptide chemically related to CCK<br>
isolated from frog skin, also antagonizes harmaline<br>
pendent tr

intracerebellar convulsants, pentylenetetrazol and pic<br>toxin.<br>Caerulein, a peptide chemically related to CCK a<br>isolated from frog skin, also antagonizes harmaline-<br>pendent tremor (Zettler, 1983) and antagonizes harn<br>line-d toxin.<br>Caerulein, a peptide chemically related to CCK and<br>isolated from frog skin, also antagonizes harmaline-de-<br>pendent tremor (Zettler, 1983) and antagonizes harma-<br>line-dependent increases in cerebellar cGMP (Kageyama<br> Caerulein, a peptide chemically related to CCK and<br>isolated from frog skin, also antagonizes harmaline-de-<br>pendent tremor (Zettler, 1983) and antagonizes harma-<br>line-dependent increases in cerebellar cGMP (Kageyama<br>and Kur isolated from frog skin, also antagonizes har<br>pendent tremor (Zettler, 1983) and antagoniz<br>line-dependent increases in cerebellar cGMP (<br>and Kurosawa, 1989). In contrast, this pepti<br>antagonize apomorphine- or methamphetami pendent tremor (Zettler, 1983) and antagonizes harma-<br>line-dependent increases in cerebellar cGMP (Kageyama<br>and Kurosawa, 1989). In contrast, this peptide did not<br>antagonize apomorphine- or methamphetamine-depend-<br>ent incr line-dependent increases in cerebellar cGMP (Kageyama conditionally). In contrast, this peptide did not 1 antagonize apomorphine- or methamphetamine-dependent increases in cerebellar cGMP (Kageyama and Kurosawa, 1989). Add and Kurosawa, 1989). In contrast, this peptide did not 1<br>antagonize apomorphine- or methamphetamine-depend-<br>ent increases in cerebellar cGMP (Kageyama and Ku-<br>rosawa, 1989). Additionally, the effects of this peptide s<br>were antagonize apomorphine- or methamphetamine-depend-<br>ent increases in cerebellar cGMP (Kageyama and Ku-<br>rosawa, 1989). Additionally, the effects of this peptide sen<br>were blocked by vagotomy, suggesting a peripheral locus lev ent increases in cerebellar cGMP (Kageyama and Kurensawa, 1989). Additionally, the effects of this peptide sextive were blocked by vagotomy, suggesting a peripheral locus level action. The differences observed for this pep rosawa, 1989). Additionally, the effects of this peptide sense were blocked by vagotomy, suggesting a peripheral locus leve of action. The differences observed for this peptide may dop well relate to a species difference b were blocked by vagotomy, suggesting a peripheral locus<br>of action. The differences observed for this peptide may<br>well relate to a species difference because caerulein was<br>studied in rats and the CCK studies were performed of action. The differences observed for this peptide may dop-<br>well relate to a species difference because caerulein was fibe-<br>studied in rats and the CCK studies were performed in 6.<br>mice. Another clear difference was the well relate to a species difference because caerulein was fib<br>studied in rats and the CCK studies were performed in<br>mice. Another clear difference was the duration of effect; siv<br>caerulein antagonized the effects of harmal studied in rats and the CCK studies were performed in<br>mice. Another clear difference was the duration of effect;<br>caerulein antagonized the effects of harmaline up to 30 C<br>h postinjection in the rat, long after the peptide mice. Another clear difference was the duration of effect;<br>caerulein antagonized the effects of harmaline up to 30<br>h postinjection in the rat, long after the peptide had been<br>degraded, whereas CCK only antagonized the effe 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 caer degraded, whereas CCK only antagonized the effects of<br>harmaline up to 1 h in the mouse. These data argue for<br>a long-term adaptive mechanism in the actions of caeru-<br>lein in the rat.<br>5. Opiates. Morphine has been shown to d graded, whereas CCK only antagonized the effects of effermaline up to 1 h in the mouse. These data argue for long-term adaptive mechanism in the actions of caeru-<br>in in the rat.<br>5. Opiates. Morphine has been shown to dose harmaline up to 1 h in the mouse. These data argue for<br>a long-term adaptive mechanism in the actions of caeru-<br>lein in the rat.<br>5. Opiates. Morphine has been shown to dose and time<br>dependently decrease cerebellar cGMP leve

(Biggio et al., 1977b; Katz and Catravas, 1976). These largest al.

EREBELLUM<br>actions were stereospecific as assessed with the stere<br>isomers of the opiate agonist viminol (Biggio et a EREBELLUM 19<br>actions were stereospecific as assessed with the stereo-<br>isomers of the opiate agonist viminol (Biggio et al.,<br>1977b). The opiate receptor antagonist, naltrexone, did 19<br>2015 actions were stereospecific as assessed with the stereo-<br>1977b). The opiate receptor antagonist, naltrexone, did<br>1977b). The opiate receptor antagonist, naltrexone, did<br>1977b). The opiate receptor antagonist, naltr notions were stereospecific as assessed with the stereo-<br>isomers of the opiate agonist viminol (Biggio et al.,<br>1977b). The opiate receptor antagonist, naltrexone, did<br>not alter basal cGMP levels but did antagonize the<br>dece actions were stereospectic as assessed with the stereo-<br>isomers of the opiate agonist viminol (Biggio et al.,<br>1977b). The opiate receptor antagonist, naltrexone, did<br>not alter basal cGMP levels but did antagonize the<br>decea 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 di not alter basal cGMP levels but did antagonize the<br>deceases elicited by opiate agonists (Biggio et al., 1977b).<br>Naloxone, at opioid receptor antagonist doses, also did<br>not alter basal cerebellar cGMP levels; however, at ex deceases elicited by opiate agonists (Biggio et al., 1977b).<br>Naloxone, at opioid receptor antagonist doses, also did<br>not alter basal cerebellar cGMP levels; however, at ex-<br>tremely high doses (60–240 mg/kg) this drug elici not alter basal cerebellar cGMP levels; however, at extremely high doses  $(60-240 \text{ mg/kg})$  this drug elicited

(Wood et al., 1988b; Wood, 1989). Pretreatments with injections of the enkephalin analogue,  $D$ -Ala<sub>2</sub>-Met-en-CCK were found to antagonize the effects of dopami-<br>CCK were found to antagonize the effects of dopami-<br>neparat dose-dependent increases in cGMP, presumably via a GABA-antagonist action (Gumulka et al., 1979b).<br>The actions of morphine were not altered by 3-acetyl-<br>pyridine lesions of the climbing fibers (Biggio et al., 1977d), were pyridine 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). T GABA-antagonist action (Gumulka et al., 1979b).<br>The actions of morphine were not altered by 3-acetyl-<br>pyridine lesions of the climbing fibers (Biggio et al.,<br>1977d), were not reproduced by direct intracerebellar<br>injections The actions of morphine were not altered by 3-acetyl-<br>pyridine lesions of the climbing fibers (Biggio et al.,<br>1977d), were not reproduced by direct intracerebellar<br>injections (Biggio et al., 1977b,d), but were reproduced<br>b pyridine 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). T 1977d), were not reproduced by direct intracerebellar<br>injections (Biggio et al., 1977b,d), but were reproduced<br>by intrastriatal injections (Biggio et al., 1977b,d). These<br>data are consistent with a modulatory effect of str mjections (Eiggio et al., 19776,0), but were reproduced<br>by intrastriatal injections (Biggio et al., 1977b,d). These<br>data are consistent with a modulatory effect of striatal<br>opioid synapses on the striatal output neurons wh opioid synapses on the striatal output neurons which<br>modulate pontocerebellar mossy fiber input to the cere-<br>bellum (fig. 4; section V.B.1). This conclusion is further<br>supported by the report (Biggio et al., 1978c) of dose opioid synapses on the striatal output neurons which<br>modulate pontocerebellar mossy fiber input to the cere-<br>bellum (fig. 4; section V.B.1). This conclusion is further<br>supported by the report (Biggio et al., 1978c) of dose modulate pontocerebellar mossy fiber input to the<br>bellum (fig. 4; section V.B.1). This conclusion is fu<br>supported by the report (Biggio et al., 1978c) of d<br>dependent decreases in cerebellar cGMP by intrasti<br>injections of t bellum (fig. 4; section V.B.1). This conclusion is further<br>supported by the report (Biggio et al., 1978c) of dose-<br>dependent decreases in cerebellar cGMP by intrastriatal<br>injections of the enkephalin analogue, D-Ala<sub>2</sub>-Met supported by the report (Biggio et al., 1978c) of dose-<br>dependent decreases in cerebellar cGMP by intrastriatal<br>injections of the enkephalin analogue, D-Ala<sub>2</sub>-Met-en-<br>kephalinamide. As with morphine, the actions of this<br>p injections of the enkephalin analogue,  $D - Ala_2 - Met-en$ bellar administration (Biggio et al., 1978c). peptide derivative were reversed by the opiate antagonist naltrexone and were not replicated by direct intracere-

in some strains and were not replicated by direct intracent-<br>bellar administration (Biggio et al., 1978c).<br>In mice, strain differences in the actions of morphine<br>on cerebellar cGMP have been reported, with increases<br>in som In mice, strain differences in the actions of morphine<br>on cerebellar cGMP have been reported, with increases<br>in some strains and decreases in others (Askew and<br>Charalampous, 1976; Racagni et al., 1979). These differ-<br>ences on cerebellar cGMP have been reported, with increases<br>in some strains and decreases in others (Askew and<br>Charalampous, 1976; Racagni et al., 1979). These differ-<br>ences may well reflect strain differences in the effects of 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 a Charaanipous, 1970, Racagin et al., 1979). These unfer-<br>ences may well reflect strain differences in the effects of<br>morphine on dopamine release within the striatum<br>(Wood and Altar, 1989; Wood and Richard, 1982; Wood,<br>1983 ences may wen renect stram unrerences in the enects of<br>morphine on dopamine release within the striatum<br>(Wood and Altar, 1989; Wood and Richard, 1982; Wood,<br>1983) because C57BL/6J mice had parallel increases in<br>striatal do (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 1983) because C57BL/6J mice had parallel increases in<br>striatal dopamine release, increased cerebellar cGMP,<br>and enhanced motor activity, whereas DBA mice had<br>decrements in striatal dopamine release and cerebellar<br>cGMP with 1979). 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).<br>During withdrawal, morphine-dependent rats possess

decrements in striatal dopamine release and cerebellar cGMP with no change in motor activity (Racagni et al., 1979).<br>
During withdrawal, morphine-dependent rats possess<br>
elevated basal cerebellar cGMP levels and are more<br> cGMP with no change in motor activity (Racagni et al., 1979).<br>
During withdrawal, morphine-dependent rats possess<br>
elevated basal cerebellar cGMP levels and are more<br>
sensitive to apomorphine-dependent increases in cGMP<br>
l 1979).<br>
During withdrawal, morphine-dependent rats posse<br>
elevated basal cerebellar CGMP levels and are mo<br>
sensitive to apomorphine-dependent increases in cGM<br>
levels (Volicer et al., 1977), again supporting an opio<br>
dopa During withdrawal, morphine-dependent rats possess<br>elevated basal cerebellar cGMP levels and are more<br>sensitive to apomorphine-dependent increases in cGMP<br>levels (Volicer et al., 1977), again supporting an opioid-<br>dopamine elevated basal cerebells<br>sensitive to apomorphin<br>levels (Volicer et al., 197<br>dopamine linkage in the<br>fiber pathway (fig. 4).<br>6. Indole modulators. maitive to apomorphine-dependent increases in cGM<br>vels (Volicer et al., 1977), again supporting an opioi<br>pamine linkage in the striato-pontocerebellar mos<br>er pathway (fig. 4).<br>6. *Indole modulators*. The cerebellum receive

levels (Volicer et al., 1977), again supporting an opioid-<br>dopamine linkage in the striato-pontocerebellar mossy<br>fiber pathway (fig. 4).<br>6. *Indole modulators*. The cerebellum receives exten-<br>sive serotonergic innervation dopamine linkage in the striato-pontocerebellar mossy<br>fiber pathway (fig. 4).<br>6. *Indole modulators*. The cerebellum receives exten-<br>sive serotonergic innervation from the raphe (Palay and<br>Chan-Palay, 1974); however, a com following the reference of 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 ef ve serotonergic innervation from the raphe (Palay and<br>nan-Palay, 1974); however, a comprehensive study of<br>rotonin receptor agonists and antagonists, for their<br>fects on cerebellar cGMP, has never been undertaken.<br>The seroto

Chan-Palay, 1974); however, a comprehensive study of<br>serotonin receptor agonists and antagonists, for their<br>effects on cerebellar cGMP, has never been undertaken.<br>The serotonin uptake inhibitor, fluoxetine, and the<br>seroton serotonin receptor agonists and antagonists, for their<br>effects on cerebellar cGMP, has never been undertaken.<br>The serotonin uptake inhibitor, fluoxetine, and the<br>serotonin precursor, 5-hydroxytryptophan, did not alter<br>basa effects on cerebellar cGMP, has never been undertaken.<br>The serotonin uptake inhibitor, fluoxetine, and the<br>serotonin precursor, 5-hydroxytryptophan, did not alter<br>basal cGMP levels (Chung, 1983). The nonselective and<br>nonsp The serotonin uptake inhibitor, fluoxetine, and the serotonin precursor, 5-hydroxytryptophan, did not alter based cGMP levels (Chung, 1983). The nonselective an nonspecific serotonin agonists lysergic acid (Burkard dal., 1 serotonin precursor, 5-hydroxytryptophan, did not alter<br>basal cGMP levels (Chung, 1983). The nonselective and<br>nonspecific serotonin agonists lysergic acid (Burkard et<br>al., 1976) and 5-methoxy-dimethyl-tryptamine (Ly-<br>koura

receptor type involved in this action is not known. In the 20<br>receptor type involved in this action is not known. In th<br>case of lysergic acid, the increases in cGMP were coun<br>teracted by the neuroleptic, haloperidol, suggesting po w<br>receptor type involved in this action is not known. In the<br>case of lysergic acid, the increases in cGMP were coun-<br>teracted by the neuroleptic, haloperidol, suggesting pos-<br>sible dopaminergic involvement (Burkard et al., 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) 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) 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 bloc teracted by the neuroleptic, haloperidol, suggesting possible dopaminergic involvement (Burkard et al., 1976)<br>while those of 5-methoxy-dimethyl-tryptamine were not<br>blocked by haloperidol, cyproheptadine, or methysergide<br>(L sible dopaminergic involvement (Burkard et al., 19<br>while those of 5-methoxy-dimethyl-tryptamine were<br>blocked by haloperidol, cyproheptadine, or methyser<br>(Lykouras et al., 1980). The serotonin antagonists, or<br>nanserin (Chun while those of 5-methoxy-dimethyl-tryptamine were not<br>blocked by haloperidol, cyproheptadine, or methysergide (Di<br>(Lykouras et al., 1980). The serotonin antagonists, cin-<br>nanserin (Chung, 1983) and cyproheptadine (Dinnenblocked by haloperidol,<br>(Lykouras et al., 1980).<br>nanserin (Chung, 1983<br>dahl and Gumulka, 19<br>levels in the cerebellum<br>In summary, little is nanserin (Chung, 1983) and cyproheptadine (Dinnen-<br>dahl and Gumulka, 1977), did not alter basal cGMP<br>levels in the cerebellum.<br>In summary, little is known of the serotonergic mod-<br>ulation of cerebellar cGMP levels; however

dahl and Gumulka, 1977), did not alter basal cGMP<br>levels in the cerebellum.<br>In summary, little is known of the serotonergic mod-<br>ulation of cerebellar cGMP levels; however, with the<br>wealth of new pharmacological tools for revels in the cerebellum.<br>In summary, little is known of the serotonergic modulation of cerebellar cGMP levels; however, with the<br>wealth of new pharmacological tools for serotonergic<br>receptor subtypes, our knowledge in thi In summary, little<br>
ulation of cerebella<br>
wealth of new phe<br>
receptor subtypes,<br>
doubtedly increase.<br>
7. Noradrenergic ation of cerebellar cGMP levels; however, with the<br>alth of new pharmacological tools for serotonergic<br>reptor subtypes, our knowledge in this area will un-<br>ubtedly increase.<br>7. *Noradrenergic modulators*. The cerebellum als

wealth of new pharmacological tools for serotonergic<br>receptor subtypes, our knowledge in this area will un-<br>doubtedly increase.<br>7. Noradrenergic modulators. The cerebellum also re-<br>ceives extensive noradrenergic innervatio receptor subtypes, our knowledge in this area will undoubtedly increase.<br>
7. Noradrenergic modulators. The cerebellum also receives extensive noradrenergic innervation from the locus coereleus (Bloom et al., 1971; Olsen a doubtedly increase.<br>
7. Noradrenergic modulators. The cerebellum also recives extensive noradrenergic innervation from the locus coereleus (Bloom et al., 1971; Olsen and Fuxe, 1971; Studies of the  $\beta$ -adrenergic agonist, 7. Noradrenergic modulators. The cerebellum also receives extensive noradrenergic innervation from the locus coereleus (Bloom et al., 1971; Olsen and Fuxe, 1971)<br>Studies of the  $\beta$ -adrenergic agonist, isoproterenol (Haid ceives extensive noradrenergic innervation from the locus coereleus (Bloom et al., 1971; Olsen and Fuxe, 1971).<br>Studies of the  $\beta$ -adrenergic agonist, isoproterenol (Haidamous et al., 1980), and the  $\beta$ -adrenergic antag Studies of the  $\beta$ -adrenergic agonist, isoproterenol (Hai-<br>damous et al., 1980), and the  $\beta$ -adrenergic antagonist,<br>propranolol (Dinnendahl and Gumulka, 1977; Narumi et<br>al., 1983), have shown no changes in basal cerebel cGMP levels.<br>In contrast, the  $\alpha_1$ -adrenergic agonists, methoxamine mous et al., 1980), and the  $\beta$ -adrenergic antagonist,<br>opranolol (Dinnendahl and Gumulka, 1977; Narumi et<br>, 1983), have shown no changes in basal cerebellar<br>:MP levels.<br>In contrast, the  $\alpha_1$ -adrenergic agonists, methox

propranolol (Dinnendahl and Gumulka, 1977; Narumi et jection.<br>
al., 1983), have shown no changes in basal cerebellar the<br>
cGMP levels. Execution E. The contrast, the  $\alpha_1$ -adrenergic agonists, methoxamine N.<br>
and phenyle al., 1983), have shown no changes in basal cerebellar<br>cGMP levels.<br>In contrast, the  $\alpha_1$ -adrenergic agonists, methoxamine<br>and phenylephrine, increased cerebellar cGMP levels, as<br>did intraventricular administration of no In contrast, the  $\alpha_1$ -adrenergic agonists, methoxamine<br>and phenylephrine, increased cerebellar cGMP levels, as<br>did intraventricular administration of norepinephrine<br>itself (Haidamous et al., 1980). The  $\alpha_2$  agonist cl did intraventricular administration of norepinephrine<br>itself (Haidamous et al., 1980). The  $\alpha_2$  agonist clonidine<br>decreased cerebellar cGMP (Haidamous et al., 1980).<br>Similarly, the  $\alpha_1$  antagonists phenoxybenzamine (C itself (Haidamous et al., 1980). The  $\alpha_2$  agonist clonidic decreased cerebellar cGMP (Haidamous et al., 198<br>Similarly, the  $\alpha_1$  antagonists phenoxybenzamine (Chuiss); Haidamous et al., 1980) and phentolamine (Hamous e decreased cerebellar cGMP (Haidamous et al., 1980).  $CGN$ <br>Similarly, the  $\alpha_1$  antagonists phenoxybenzamine (Chung, dog<br>1983; Haidamous et al., 1980) and phentolamine (Hai-haridamous et al., 1980) decreased cGMP in the ra Similarly, the  $\alpha_1$  antagonists phenoxybenzamine (Chung, dog<br>1983; Haidamous et al., 1980) and phentolamine (Hai-<br>damous et al., 1980) decreased cGMP in the rat cerebel-<br>lum. However, phentolamine has been reported not damous et al., 1980) decreased cGMP in the rat cerebel-<br>lum. However, phentolamine has been reported not to<br>alter cGMP in the mouse cerebellum (Dinnendahl and<br>Gumulka, 1977). mous et al., 1980) decreased cGMP in the rat cerebel-<br>m. However, phentolamine has been reported not to 194<br>ter cGMP in the mouse cerebellum (Dinnendahl and per<br>mulka, 1977).<br>The  $\alpha_2$  antagonist, yohimbine, and the mixe

hum. However, phentolamine has been reported not to<br>alter cGMP in the mouse cerebellum (Dinnendahl and per<br>Gumulka, 1977).<br>The  $\alpha_2$  antagonist, yohimbine, and the mixed  $\alpha_1/\alpha_2$  ap<br>antagonist, piperoxan, did not alter cerebellum (Haidamous et al., 1980).<br>In toto, it appears from these studies that a noradre-The  $\alpha_2$  antagonist, yohimbine, and the mixed  $\alpha_1/\alpha_2$ <br>antagonist, piperoxan, did not alter cGMP levels in the<br>cerebellum (Haidamous et al., 1980).<br>In toto, it appears from these studies that a noradre-<br>nergic fiber i antagonist, piperoxan, did not alter cGMP levels in the

antagonist, piperoxan, did not alter cGMP levels in the<br>cerebellum (Haidamous et al., 1980).<br>In toto, it appears from these studies that a noradre<br>nergic fiber input to the cerebellum innervates  $\alpha_1$ -adre<br>nergic recepto cerebellum (Haidamous et al., 1980).<br>
In toto, it appears from these studies that a noradre-<br>
nergic fiber input to the cerebellum innervates  $\alpha_1$ -adre-<br>
nergic receptors which, when activated, augment cere-<br>
bellar cGM In toto, it appears from these studies that a noradre-<br>nergic fiber input to the cerebellum innervates  $\alpha_1$ -adre-<br>nergic receptors which, when activated, augment cere-<br>bellar cGMP content. Some data also suggest that th mergic fiber input to the cerebellum innervates  $\alpha_1$ -adre-<br>nergic receptors which, when activated, augment cere-<br>bellar cGMP content. Some data also suggest that there<br>may be a basal ongoing tone to this noradrenergic i bellar cGMP content. Some data also suggest that there may be a basal ongoing tone to this noradrenergic input.<br>Consistent with these data are observations that NMDA augments norepinephrine release from cerebellar slices, may be a basal ongoing tone to this noradrenergic input.<br>Consistent with these data are observations that NMDA<br>augments norepinephrine release from cerebellar slices,<br>actions blocked both by competitive and noncompetitive<br> Consistent with these data are observations that NMDA actions blocked both by competitive and noncompetitive<br>NMDA receptor antagonists (Yi et al., 1988). An exten-<br>sion of these data are the observations that the nonse-<br>lective  $\alpha_1$  antagonist, clozapine, and the selective augments norepinephrine release from cerebellar slices,<br>actions blocked both by competitive and noncompetitive<br>NMDA receptor antagonists (Yi et al., 1988). An exten-<br>sion of these data are the observations that the nonseactions blocked both by competitive and noncompetitive NMDA receptor antagonists (Yi et al., 1988). An extension of these data are the observations that the nonselective  $\alpha_1$  antagonist, clozapine, and the selective  $\alpha$ NMDA receptor antagonists (Yi et al., 1988). An extension of these data are the observations that the nonselective  $\alpha_1$  antagonist, clozapine, and the selective  $\alpha_1$  is antagonist, WB-4101, both block increases in cer sion of these data are the observations that the nonse-<br>lective  $\alpha_1$  antagonist, clozapine, and the selective  $\alpha_1$ <br>antagonist, WB-4101, both block increases in cerebellar<br>cGMP, in vivo, induced by NMDA receptor activa lective  $\alpha_1$  antagonist, clozapine, and the selective  $\alpha_1$  is antagonist, WB-4101, both block increases in cerebellar cGMP, in vivo, induced by NMDA receptor activation but not quisqualate receptor activation (Rao et and CGMP, in vivo, induced by NMDA receptor activation<br>cGMP, in vivo, induced by NMDA receptor activation<br>but not quisqualate receptor activation (Rao et al., 1990i;<br>Wood and Rao, 1990; section III.B.6). These data are all but not quisqualat<br>Wood and Rao, 1:<br>consistent with a<br>norepinephrine re<br>to the cerebellum

dahl and Gumulka, 1977), did not alter basal  $cGMP$  atrial naturistic factor which increased  $cGMP$  levels in levels in the cerebellum.<br>In summary, little is known of the serotonergic mod-<br>ulation of cerebellar  $cGMP$  levels VI. Miscellaneous **Pharmacological Agents** VI. Miscellaneous Pharmacological Agents<br>A number of miscellaneous pharmacological agents<br>we been studied for their effects on cerebellar cGMP D<br>VI. Miscellaneous Pharmacological Agents<br>A number of miscellaneous pharmacological agents<br>have been studied for their effects on cerebellar cGMP<br>levels. These compounds include the antihistaminics, VI. Miscellaneous Pharmacological Agents<br>A number of miscellaneous pharmacological agents<br>have been studied for their effects on cerebellar cGMP<br>levels. These compounds include the antihistaminics,<br>diphenhydramine and anta A number of miscellaneous pharmacological agents<br>have been studied for their effects on cerebellar cGMP<br>levels. These compounds include the antihistaminics,<br>diphenhydramine and antazoline, which were inactive<br>(Dinnendahl a levels. These compounds include the antihistaminics, diphenhydramine and antazoline, which were inactive (Dinnendahl and Gumulka, 1977); the prostaglandin synthetase inhibitor, indomethacin, which was inactive levels. These compounds include the antihistaminics,<br>diphenhydramine and antazoline, which were inactive<br>(Dinnendahl and Gumulka, 1977); the prostaglandin syn-<br>thetase inhibitor, indomethacin, which was inactive<br>(Dinnendah diphenhydramine and antazoline, which were inactive<br>
(Dinnendahl and Gumulka, 1977); the prostaglandin syn-<br>
thetase inhibitor, indomethacin, which was inactive<br>
(Dinnendahl and Gumulka, 1977; Mao et al. 1974a); and<br>
atria (Dinnendahl and Gumulka, 1977); the prostaglandin syn-<br>thetase inhibitor, indomethacin, which was inactive<br>(Dinnendahl and Gumulka, 1977; Mao et al. 1974a); and<br>atrial naturistic factor which increased cGMP levels in<br>granu thetase inhibitor, indomethacin, which was inact<br>(Dinnendahl and Gumulka, 1977; Mao et al. 1974a); a<br>atrial naturistic factor which increased cGMP levels<br>granule cell cultures (Hoffman et al., 1989b) and in v.<br>after intrac (Dinnendahl and G<br>atrial naturistic fa<br>granule cell culture<br>after intracerebella<br>lished observations granule cell cultures (Hoffman et al., 1989b) and in vivo<br>after intracerebellar administration (P. L. Wood, unpub-<br>lished observations).<br>**VII. Conclusions** 

From the great array of pharmacological data pre-Sented observations).<br>
VII. Conclusions<br>
From the great array of pharmacological data pre-<br>
sented in this review can be distilled several key features<br>
of the transduction mechanisms modulating cerebellar VII. Conclusions<br>From the great array of pharmacological data pre-<br>sented in this review can be distilled several key features<br>of the transduction mechanisms modulating cerebellar<br>cGMP levels. The EAA pathways within and a From the great array of pharmacological data pre-<br>sented in this review can be distilled several key features<br>of the transduction mechanisms modulating cerebellar<br>cGMP levels. The EAA pathways within and afferent to<br>the c 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 cer of the transduction mechanisms modulating cerebellar<br>cGMP levels. The EAA pathways within and afferent to<br>the cerebellum are key focal points receiving inputs from<br>dopaminergic, cholinergic, and peptidergic neuronal pro-<br>j cGMP levels. The EAA pathways within and afferent to<br>the cerebellum are key focal points receiving inputs from<br>dopaminergic, cholinergic, and peptidergic neuronal pro-<br>jections. The EAA receptor subtype involved in vivo i the cerebellum are key focal points receiving inputs from<br>dopaminergic, cholinergic, and peptidergic neuronal pro-<br>jections. The EAA receptor subtype involved in vivo in<br>the postsynaptic transduction of these diverse input dopaminergic, cholinergic, and peptidergic neuronal projections. The EAA receptor subtype involved in vivo in<br>the postsynaptic transduction of these diverse inputs to<br>EAA-utilizing pathways appears mainly to involve<br>NMDA-t declions. The EAA receptor subtype involved in vivo in<br>the postsynaptic transduction of these diverse inputs to<br>EAA-utilizing pathways appears mainly to involve<br>NMDA-type EAA receptors. This hypothesis comes from<br>the obser the postsynaptic transduction of these diverse inputs to EAA-utilizing pathways appears mainly to involved NMDA-type EAA receptors. This hypothesis comes from the observations that competitive NMDA antagonist block locomot EAA-utilizing pathways appears mainly to involve<br>
NMDA-type EAA receptors. This hypothesis comes from<br>
the observations that competitive NMDA antagonists<br>
block locomotor-dependent increases in cGMP (Mc-<br>
Caslin and Morga NMDA-type EAA receptors. This hypothesis comes from<br>the observations that competitive NMDA antagonists<br>block locomotor-dependent increases in cGMP (Mc-<br>Caslin and Morgan, 1986b,c) and block increases in<br>cGMP elicited by ph 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 dopamin 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 CGINIP encited by pharmacological potentiation of en-<br>dogenous EAA release by climbing fiber activation with<br>harmaline (Wood et al., 1982, 1989c,d, 1990a,b), activa-<br>tion of mossy fibers with oxotremorine (Wood et al.,<br>198 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., 19 tion 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 1982), or removal of inhibitory GABAergic inputs with<br>pentylenetetrazol (Ferrendelli et al., 1980; Wood et al.,<br>1990a). The anatomical locus of NMDA actions also<br>appears to be very specific in that the major portion of<br>NM 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 1990a). The anatomical locus of NMDA actions also<br>appears to be very specific in that the major portion of<br>NMDA effects on cerebellar cGMP appear to be me-<br>diated by modulation of cerebellar norepinephrine re-<br>lease (Marwa diated by modulation of cerebellar norepinephrine re-<br>lease (Marwaha et al., 1980; 1981; Rao et al., 1990h;<br>Wood and Rao, 1990). These effects appear to be finally<br>dependent upon  $\alpha_1$  receptor activation of postsynaptic NMDA effects on cerebellar cGMP appear to be me-<br>diated by modulation of cerebellar norepinephrine re-<br>lease (Marwaha et al., 1980; 1981; Rao et al., 1990h;<br>Wood and Rao, 1990). These effects appear to be finally<br>dependen diated by modulation of cerebellar norepinephrine re-<br>lease (Marwaha et al., 1980; 1981; Rao et al., 1990h;<br>Wood and Rao, 1990). These effects appear to be finally<br>dependent upon  $\alpha_1$  receptor activation of postsynaptic lease (Marwaha et al., 1980; 1981; Rao et al., 1990h;<br>Wood and Rao, 1990). These effects appear to be finally<br>dependent upon  $\alpha_1$  receptor activation of postsynaptic<br>neurons (fig. 5); the residual (20–30%) activity of N wood and raao, 1990). I hese effects appear to be finally dependent upon  $\alpha_1$  receptor activation of postsynaptic neurons (fig. 5); the residual (20–30%) activity of NMDA on cGMP levels remaining after  $\alpha_1$  blockade p neurons (fig. 5); the re<br>on cGMP levels remai<br>involves NMDA activ<br>(fig. 5; Favaron et al.,<br>leweski et al., 1987).<br>The other general 1 on cGMP levels remaining after  $\alpha_1$  blockade presumably<br>involves NMDA activation of receptors on granule cells<br>(fig. 5; Favaron et al., 1988; Novelli et al., 1987; Wrob-<br>leweski et al., 1987).<br>The other general feature

involves NMDA activation of receptors on granule cells<br>(fig. 5; Favaron et al., 1988; Novelli et al., 1987; Wrob-<br>leweski et al., 1987).<br>The other general feature of this system is that aug-<br>mentation of cerebellar cGMP by (fig. 5; Favaron et al., 1988; Novelli et al., 1987; Wrobleweski et al., 1987).<br>
The other general feature of this system is that aug-<br>
mentation of cerebellar cGMP by EAA receptors and,<br>
therefore, all afferents acting th involves prior synthesis 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 recept mentation of cerebellar cGMP by EAA receptors and,<br>therefore, all afferents acting through EAA pathways<br>involves prior synthesis of NO. This generation of NO<br>by EAA receptor-bearing neurons leads to a tremendous<br>amplificat diversion. The anti-metally diversity of No. This generation of NO<br>by EAA receptor-bearing neurons leads to a tremendous<br>amplification system in that NO can diffuse to a wide<br>diversity of neuronal and glial cell types as w the profit synthesis of NO. This generation of NC<br>by EAA receptor-bearing neurons leads to a tremendous<br>amplification system in that NO can diffuse to a widd<br>diversity of neuronal and glial cell types as well as nerve<br>term by EAA receptor-bearing neurons leads to a tremendous<br>amplification system in that NO can diffuse to a wide<br>diversity of neuronal and glial cell types as well as nerve<br>terminals where it stimulates guanylate cyclase to gen amplification system in that NO can diffuse to a wide<br>diversity of neuronal and glial cell types as well as nerve<br>terminals where it stimulates guanylate cyclase to gen-<br>erate cGMP (fig. 5). The diverse targets where cGMP<br> diversity of neuronal and glial cell types as well as nerve<br>terminals where it stimulates guanylate cyclase to gen-<br>erate cGMP (fig. 5). The diverse targets where cGMP<br>then acts remain to be defined; however, the diversity

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The externate activity in granule and Purkinje cell populations with a resultant activation of guanylate cyclase and cGMP synthesis in diverse cell 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 diffu Populations after diffusion of the NMDA augmentation of NO synthesis activation of guanylate cyclase and cGMP synthesis in diverse cell<br>populations after diffusion of NO. In the case of Purkinje cells, the<br>NMDA modulation activation of guanylate cyclase and cGMP synthesis in diverse cell<br>populations after diffusion of NO. In the case of Purkinje cells, the<br>NMDA modulation appears to be indirect via effecting norepinephrine<br>release first. Ar activation of guanylate cyclase and cGMP synthesis in diverse corpopulations after diffusion of NO. In the case of Purkinje cells, the NMDA modulation appears to be indirect via effecting norepinephrine.<br>The release first.

populations arter dirtusion of NO. In the case of Furkinge cells, the<br>NMDA modulation appears to be indirect via effecting norepinephrine<br>release first. Arg, arginine; DA, dopamine; NE, norepinephrine.<br>chter et al., 1980) release first. Arg, arginine; DA, dopamine; NE, norepinephrine.<br>release first. Arg, arginine; DA, dopamine; NE, norepinephrine.<br>chter et al., 1980) offers targets worthy of study. Addi-<br>tionally the subsequent steps leadin chter et al., 1980) offers targets v<br>tionally the subsequent steps le<br>nuclear protooncogenes, such as<br>definition (Szekely et al., 1989).<br>As a large number of positive re Let et al., 1980) offers targets worthy of study. Addi-<br>
As a large protooncogenes, such as c-fos, require clearer<br>
finition (Szekely et al., 1989).<br>
As a large number of positive regulatory inputs appear<br>
act via EAA-util

to act via EAA-utilizing synapses to augment cerebellar<br>definition (Szekely et al., 1989).<br>As a large number of positive regulatory inputs appear<br>to act via EAA-utilizing synapses to augment cerebellar<br>cGMP, a number of in definition (Szekely et al., 1989).<br>
As a large number of positive regulatory inputs appear<br>
to act via EAA-utilizing synapses to augment cerebellar<br>
cGMP, a number of inhibitory influences appear to act<br>
via inhibitory GA As a large number of positive regulatory inputs appear<br>to act via EAA-utilizing synapses to augment cerebellar<br>cGMP, a number of inhibitory influences appear to act<br>via inhibitory GABAergic interneurons in the cerebellum<br> to act via EAA-utilizing synapses to augment cerebellar<br>cGMP, a number of inhibitory influences appear to act<br>via inhibitory GABAergic interneurons in the cerebellum<br>(Biggio et al., 1977a,d; Mohler et al., 1981). A notable cGMP, a number of inhibitory influences appear to a<br>via inhibitory GABAergic interneurons in the cerebellu<br>(Biggio et al., 1977a,d; Mohler et al., 1981). A notab<br>exception to this is the depressant actions of ethan<br>that ar via inhibitory GABAergic interneurons in the cerebellum<br>(Biggio et al., 1977a,d; Mohler et al., 1981). A notable<br>exception to this is the depressant actions of ethanol<br>that are mediated by NMDA receptor antagonism (Hoff-<br>m iggio et al., 1977a,d; Mohler et al., 1981). A notable<br>
ception to this is the depressant actions of ethanol<br>
at are mediated by NMDA receptor antagonism (Hoff-<br>
and et al., 1989a,b).<br>
In summary, the neuronal activity of

exception to this is the depressant actions of ethanol<br>that are mediated by NMDA receptor antagonism (Hoff-<br>man et al., 1989a,b).<br>In summary, the neuronal activity of the cerebellum<br>involves a delicate balance between EAA that are mediated by NMDA receptor antagonism (Hoffman et al., 1989a,b).<br>
In summary, the neuronal activity of the cerebellum<br>
involves a delicate balance between EAA and GABAergic<br>
neurons, both possessing extensive and d man et al., 1989a,b).<br>In summary, the neuronal activity of the cerebellu<br>involves a delicate balance between EAA and GABAerg<br>neurons, both possessing extensive and diverse synapt<br>inputs. The actions of these two major neur In summary, the neuronal activity of the cerebellum<br>involves a delicate balance between EAA and GABAergic<br>neurons, both possessing extensive and diverse synaptic<br>inputs. The actions of these two major neurotransmitter<br>syst involves a delicate balance between EAA and GABAer<sub>i</sub><br>neurons, both possessing extensive and diverse synap<br>inputs. The actions of these two major neurotransmitt<br>systems have been extensively characterized at the<br>ceptor lev neurons, both possessing extensive and diverse synaptinguts. The actions of these two major neurotransmit systems have been extensively characterized at the ceptor level, and as presented in this review, our knowedge of su ing. Systems have been extensively characterized at the re-<br> *Achos equent* is and as presented in this review, our knowl-<br> *Acknowledgments.* I thank my coworkers who have collaborated with<br> *Acknowledgments.* I thank my cowor

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V. Nair, H. S. Kim, D. J. Steel, Dr. C. A. Altar, Dr. B. Petrack, Dr. J. MUELLER, the cerebellum. These investigators included J. W. Richard, Dr. N. P. W. Nair, H. S. Kim, D. J. Steel, Dr. C. A. Altar, Dr. B. Petrack, Dr. J. Acknowledgments. I thank my coworkers who have collaborated with<br>me throughout 10 years in investigating second messenger function in<br>the cerebellum. These investigators included J. W. Richard, Dr. N. P.<br>V. Nair, H. S. Kim Acknowledgments. I thank my coworkers who have collaborated with me throughout 10 years in investigating second messenger function in the cerebellum. These investigators included J. W. Richard, Dr. N. P. V. Nair, H. S. Kim me through<br>the cerebell<br>V. Nair, H.<br>Lehmann, I<br>S. Iyengar.

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