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Gammahydroxybutyrate: An Overview of the Pros and Cons for it Being a Neurotransmitter And/Or a Useful Therapeutic Agent

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CASH, C. D. *Gammahydroxybutyrate: an overview of the pros and cons for it being a neurotransmitter and/or a useful therapeutic agent*. NEUROSCI BIOBEHAV REV **18**(2) 291–304, 1994.—Gamma-hydroxybutyrate (GHB) is a catabolite in brain of γ-aminobutyrate (GABA) and is also found in nonneuronal tissues. It is present in the brain at about one thousandth of the concentration of its parent compound. High affinity and specific uptake, and energy dependent transport systems for GHB have been described in brain in addition to a class of high affinity binding sites, functional at a rather unphysiologically low pH.

Administration of large doses of GHB to animals and man leads to sedation, and at the highest doses, anaesthesia. These effects are prominent when GHB brain levels are over one hundred-fold the endogenous levels. In some animals, GHB administration also induces an electroencephalographic and behavioural changes resembling that of human petit mal epilepsy. GHB has been used in man as an anaesthetic adjuvant. GHB lowers cerebral energy requirements and may play a neuroprotective role. Administered GHB profoundly effects the cerebral dopaminergic system by a mechanism which remains to be unravelled. GHB has been tested with success on alcoholic patients where it attenuates the withdrawal syndrome. It is indicated here that in this situation, it may owe its effect by acting as a pro-drug of the neurotransmitter GABA into which it can be transformed. As administration of GHB, a $GABA_B$ receptor agonist and a natural opioid peptide all elicit similar abnormal EEG phenomena, it may be suggested that they are acting via a common pathway. The petit mal epileptic effects of GHB might be ascribed to its direct, or indirect agonist properties after transformation to a pool of GABA at the $GABA_B$ receptor or via interactions at its own binding sites linked to a similar series of biochemical events. Some anticonvulsant drugs, the opiate antagonist naloxone and a synthetic structural GHB analogue antagonise certain behavioural effects of GHB administration. It is postulated that GHB exerts some of its effects via transformation to GABA pools, and that substances which inhibit this process antagonise its effects by blocking GABA formation. GHB has been proposed as a neurotransmitter, although straightforward evidence for this role is lacking. Evidence for and against GHB, as a neurotransmitter, is reviewed here together with a discussion of its potential as a therapeutically useful drug.

Gammahydroxybutyrate Neurotransmitter Therapeutic agent GABA receptors

INTRODUCTION

GABA is now generally accepted as the major inhibitory neurotransmitter of the central nervous system (CNS). It is derived principally from glutamate (Glu) which itself is an excitatory neurotransmitter and interacts with several receptor subclasses which in turn provoke various neurophysiological events.

Endogenous GHB which appears to be formed from GABA is present in brain tissue at micromolar concentrations whereas its potential precursor amino acids are found in millimolar concentrations.

Unlike GABA, Glu, or other neurotransmitters, GHB is able to traverse the blood–brain barrier after peripheral administration, and in high doses, it induces behavioural responses including sedation and eventually anaesthesia accompanied in some animal species with an EEG response which is similar to that seen in human petit mal epilepsy.

GHB is also found in nonneural tissues; indeed the kidney contains more than 10 times the concentration found in brain

tissue whereas heart and muscle display 5-times greater levels (134). However, very little is known about the biochemical role for GHB outside of the brain.

In 1964, Laborit presented a strong case for the use of GHB in anaesthesia and in psychiatry due to its low toxicity and lack of side effects (103). Thirteen years later, Snead reviewed the evidence that endogenous GHB might be involved in the modulation of dopaminergic neuronal activity, sleep regulation and in some pathologic states (170). Another 10 yr elapsed before Vayer et al. proposed that GHB may play a neurotransmitter role (200).This belief has recently been reinforced by Tunnicliff (189). Mamelak has proposed that GHB is a major endogenous inhibitor of energy metabolism and thus may play a protective role when energy supplies are limited in both neuronal and peripheral tissues (122).

In this review, my concern will center around the published data to provide the reader with a clearer view as to whether or not endogenous GHB plays a physiological role, possibly as a neurotransmitter and/or in pathology. In addition, I will examine its further potential as a therapeutic agent. With this in mind, I have taken into account various mechanisms where a role of GHB has been implicated or proposed. An effort has been made here to deal with the existing controversies pertaining to the mode of action of GHB.

THE IN VITRO BIOCHEMISTRY OF GHB

It is widely accepted that a neurotransmitter fulfils certain biochemical criteria, namely those of high affinity and specific binding, uptake and release. From such a standpoint, the major biochemical data of GHB in the brain are presented below and are grouped into two categories, firstly those that, in the author's view, support its role as a neurotransmitter, and secondly, results of considerable physiological relevance that do not commit or omit a role for GHB as a neurotransmitter.

PRO-NEUROTRANSMITTER DATA

An apparently specific enzyme for GHB biosynthesis from GABA via succinic semialdehyde (SSA) has been described in both rat (150) and human brain (30) and this molecule is released from preloaded brain slices under depolarising conditions, a process that requires Ca^{2+} and is blocked by tetrodotoxin (118). In brain tissue culture, there exist GHB binding sites which are exclusive to neurones as opposed to glia (87). Subcellular fractionation of rat brain indicates that this binding is principally localised in the synaptosomal fraction (120).

GHB is unevenly distributed in the rat brain, and its concentrations do not closely follow that of its proposed biosynthetic enzyme: "specific" succinic semialdehyde reductase (197). However, endogenous GHB is found at the highest concentrations first in the cytosol, and, second, in the synaptosomal fraction prepared from rat brain. Its addition to the homogenising medium before tissue fractionation results in its enrichment in synaptosomes (166).

DATA WHICH ARE NOT POSITIVELY SUPPORTIVE OF A NEUROTRANSMITTER ROLE

Binding sites for GHB exist both in rat (12), and human (179) brain membranes. In rat brain, high and low affinity components of these binding sites are characterised. The high affinity binding has a K_d of 95 nM at the pH optimum of 5.5 with no affinity for GABA or baclofen (12). This could qualify GHB as a neurotransmitter if the pH optimum for binding were in the neutral physiological range. In addition, there exists a Na^+-dependent uptake system operating at a K_m value of about 50 μM which is 20 times higher than the endogenous brain concentration of GHB. Moreover, GABA competes with this transport system (13). In striatal slices, a K_m value of 700 μM has been reported (77).

The enzymes that are able to catabolise GHB are not specific and their K_m values are much higher than the endogenous GHB concentration (93). In cortical brain tissue slices, 0.5 μM GHB stimulates the rate of O_2 consumption in the presence of glucose. In the absence of glucose, GHB is unable to support respiration (187). Thus, its catabolism does not seem to involve a single enzymatic step but is rather linked to a general energy requiring metabolic process.

GHB levels are higher in postmortem human brain taken from individuals with Huntingdon's disease (3), and they are increased in an animal model of this disease induced by striatal injection of the neurotoxin, kainic acid (4). These data suggest disposal of GHB in the neurones because this disease is characterised by extensive striatal neuronal loss (99).

Application of 1 mM GHB to cultured neurones from the rat causes hyperpolarization which is reversed by the GABA receptor antagonist, bicuculline (88). In guinea-pig pars compacta neurones, derived from the substantia nigra, GHB at a minimum concentration of 100 μM hyperpolarises the cell membrane and facilitates Ca^{2+} conductance (75). At this same concentration, GHB antagonises the depolarisation-induced release of newly synthesised dopamine from rat brain striatal slices (26). Thus, GHB at a concentration that might not be attainable in the brain under physiological conditions can interact directly or indirectly with the gabaergic and dopaminergic systems.

A selective though weak affinity of GHB for $GABA_B$ receptors has recently been reported (IC_{50} = 150 μM) (14), although previous data showed that GHB cannot compete with GABA at this site (168). Activation of the $GABA_B$ receptor by GHB, in vitro, hyperpolarizes hippocampal neurones (212) and depresses synaptic potentials in hippocampal slices (211). In addition, GHB binds to a population of sites that show high affinity for trans-γ-hydroxycrontonic acid (THCA) (81), a substance that has been identified in both renal (135) and brain tissues (196). The possible significance of this interaction has not been defined, although THCA may be a catabolite of GHB.

Hippocampal slices incubated with about 0.5 mM GHB result in a significant increase in both intracellular cyclic GMP and inositol phosphates levels (199). Because a major route for cyclic GMP synthesis is via activation of soluble guanylyl cyclase by nitric oxide formation generated by agonist induced calcium entry through the *N*-methyl D-aspartate category of glutamate receptors (24,60,61), and as nitric oxide can stimulate phosphoinositol hydrolysis (163), it would seem that in this pathway GHB exhibits a neuroexcitatory role.

These data taken alone certainly are not of much consequence in delineating GHB as a possible neurotransmitter in the CNS. Nevertheless, although most established neurotransmitters bind optimally to their receptors at a neutral pH, the binding of 1,3,4,5-tetrakisphosphate to its cerebellar receptor has been found to be optimal at pH 5.0 (46). Moreover, GHB is a simple molecule which possesses only an alcohol and a carboxyl as functional groups. This latter may be required to exist in the protonated form for recognition and binding.

BIOCHEMICAL CORRELATIONS OF GHB ADMINISTRATION

GHB is a psychoactive drug that manifests its effects when administered intravenously or even taken orally and as such

differs fundamentally from established neurotransmitters that do not normally pass the blood–brain barrier. Indeed, it may well be present in the food chain, for example, the presence of γ-butyrolactone (GBL), its lactone precursor, has been detected in wine (128). Because GBL is often employed as a pro-drug that is efficient, indeed with a higher availability (110) than the active compound GHB (146) into which it can be rapidly converted (148) by a blood-born γ-lactonase (54), it will be specified which substance is administered. None of the following data can thus be considered as directly indicating or negating a neurotransmitter role for GHB because the doses employed other than that required for the pyretic effect referred to below would be expected to induce brain levels of some two orders of magnitude higher than the normal endogenous concentration.

PHARMACOKINETIC CONSIDERATIONS

Intravenous injection of about 3.5 mmol /Kg GHB (an anaesthetic dose) to the cat resulted in a brain GHB levels of about 0.7 μM and about double this value in the blood (147). A similar result was obtained in dogs, and with a rapid outflow of GHB from the brain to the cerebrospinal fluid (159). Thus, GHB passes readily from the bloodstream to the brain and gives rise to a concentration of over 100 times its normal endogenous level but does not appear to be actively taken up or retained by brain.

INTERACTIONS WITH THE DOPAMINERGIC, SEROTONERGIC AND GABAERGIC SYSTEMS

Brain dopamine levels are increased by GHB administration. In rats, these levels were doubled 1 h after IV injection of 20 mmol GHB (62). Lower doses also increase these levels but are without effect on the serotonergic system (131). Mice perfused with 7.5 mmol/Kg GBL intraperitonealy, displayed increased immunostaining for tyrosine hydroxylase in the striata (76). Subsequent to GHB administration, the kinetic constants of tyrosine hydroxylase are unchanged, but the decreased affinity that it displays for its pteridine cofactor after treatment with the neuroleptic drug, haloperidol, is antagonised by GHB pretreatment (214). However, in awake rats, subanaesthetic doses of GHB stimulate the firing rate of nigral dopaminergic neurones, whereas high doses suppress the firing (44). In in vivo microdialysis experiments, low doses of GHB inhibit dopamine release whereas high doses strongly increase it (78). Administration of the $GABA_B$ receptor agonist, baclofen, induces a similar dopaminergic response to that of GHB administration (38). In adolescent rats, a high dose of GHB increases the rate of synthesis and degradation of serotonin whereas in neonatal animals it had no effect (82). However, chronic, high dose administration of GBL to mice appears to downregulate the gabarergic system (63).

When GHB is microiontophoretically applied to cortical neurones of the rabbit, it depresses their firing, an effect that is blocked by the $GABA_A$ receptor antagonist, biccuculline (100), although prior treatment of rats with high doses of GHB failed to modify the ex-vivo characteristics of this receptor (157).

INTERACTIONS WITH THE NITRINERGIC/CYCLIC GMP SYSTEM

Injection of GHB in rats at a dose of 10 mmol/Kg induces a sustained hypertensive effect (90). The cyclic GMP content of rat brain hippocampus was approximately doubled after administration of 5 mmol/Kg GHB (199), whereas the cerebellar levels of cyclic GMP are considerably reduced (14).

INTERACTIONS WITH THE OPIOID SYSTEM

Administration to rats of an anaesthetic dose of GHB increases the brain opioid peptide content (107). As opiate antagonists effect the behavioural attributes of GHB administration, this subject is further discussed below.

METABOLIC EFFECTS

Profound effects of GHB on energy metabolism are observed. Injection of 5 mmol/Kg GHB in the rat appears to specifically stimulate the pentose phosphate shunt pathway (187). A similar dose of GHB or GBL profoundly diminishes the rate of cerebral glucose utilisation (65,116,210). Whereas high doses of GHB lowered the body temperature (104), a low dose, (0.1 mmol/Kg) induced a pyretic effect (92).

HYPOTHETICAL EXPLANATIONS FOR THE BIOCHEMICAL IN VITRO AND IN VIVO EFFECTS

It is well known that GHB can inhibit the depolarisation-induced release of newly synthesised dopamine from brain tissue (26) and this, in part, might explain the increased brain levels after its administration. Such an effect may be due to its inhibitory action on the cell body of dopamine-releasing neurones (2) acting possibly through GHB-uptake by these cells. It might, on the other hand, be a result of $GABA_B$ receptor activation because these effects are mimicked by baclofen (38). In the latter case, it could be either due to a direct action of GHB on this receptor (14), or, after its metabolic transformation to an appropriate pool of neuroactive GABA. However, the $GABA_B$ receptor is coupled to a GTP-binding protein (84), an effector site that is shared by at least one other neurotransmitter (5). Thus GHB might be acting at its specific binding sites causing a similar cascade of G-protein-mediated events. This finds support because previous studies have shown that GTP inhibits GHB binding (164), although, a contribution by, or synergy between both $GABA_B$ receptors and GHB binding sites cannot be ruled out. The increased opioid peptide levels induced by GHB (107) might also be a factor involved in the stimulation of dopamine synthesis (15).

The serotonin-increasing effects of high doses of GHB are more likely due to its interaction with its own binding sites because GHB-binding sites increase postnatally (12) whereas this serotonergic response is absent at birth (82).

Reversible hypertension can be induced by inhibition of nitric oxide synthesis (59). GHB reduces the cyclic GMP content of the cerebellum, a brain region where GHB binding sites are almost absent (79). The principal activator of soluble guanylyl cyclase is now thought to be nitric oxide (24). If this phenomenon is applicable to peripheral tissues where GHB binding sites are also absent, it could be postulated that GHB decreases nitric oxide synthesis by an as yet unknown nonneuronal mechanism.

The increase in the cyclic GMP level observed in the hippocampus after GHB treatment is more probably due to a neuronal stimulation of nitric oxide synthesis via GHB binding sites which are abundant in this region (79). Although nitric oxide synthase-containing neurones are not very prevalent in this tissue, a majority of these neurones also contain GABA (193). The biochemical basis of this phenomenon remains to be elucidated but behavioural data indicate that a GHB-mediated event is associated with the activation of the *N*-

methyl-D-aspartate category of glutamate receptors (9). Activation of these receptors in brain tissue opens a Ca^{2+} channel (50). Ca^{2+} is a requirement both for the synthesis of neuronal nitric oxide (97) and for agonist binding to the $GABA_B$ receptor (83). Thus there is, at least in part, a tenuous biochemical relationship for the cyclic nucleotide and gabaergic events.

The mechanism by which high doses of GHB increase brain opioid peptide content cannot be facilely explained as a gabaergic process because the $GABA_B$ agonist, baclofen potentiates the K^+-evoked release of methionine-enkephalin from rat brain striatal slices (151), whereas the $GABA_A$ agonist, muscimol decreases this release (136). Because administration of the general opioid antagonist, naloxone, overcomes many of the biochemical (37,198), and behavioural (174) effects of GHB administration, the effects of GHB must nevertheless be interrelated with the endogenous opioid system.

Naloxone antagonises the enkephalin-stimulated increase in rat brain dopamine synthesis (15). In addition, it blocks the increase in dopamine accumulation and release, induced by application of GHB to the rat brain by in vivo microdialysis (78) Thus it would appear that an effect on the opioid system is a prerequisite for the dopaminergic effects. Dopamine receptor stimulation elevates depolarisation-induced enkephalin release (114), whereas GHB administration increases brain opioid content (107). This may be attributed to the increase in dopamine synthesis in the striatum induced by GHB administration (62) and inhibition of its release (26). As naloxone blocks, in particular, the EEG effects of GHB administration (vide infra), it might be expected that GHB induces enkaphalin release by an as yet unknown mechanism, perhaps through interactions with its own binding sites. Another possibility is that GHB is transformed to a pool(s) of GABA which then modulate enkephalin release (17,18,161), If this is true, then gabaergic activation preceeds both the opioid and dopaminergic events.

The decrease in energy metabolism caused by administration of GHB could be related to an increased availability of reduced NADPH due to its oxidation catalised by aldehyde reductase working as a dehydrogenase (95). However, this hypothesis is discordant with the data that indicates that the pentose phosphate shunt pathway is stimulated by GHB administration (187), because this metabolic route requires oxidised $NADP^+$ for its functioning. It could however, explain the lowering of body temperature induced by high doses of GHB, although the mechanism by which naloxone overcomes some of the GHB-induced metabolic effecs (37) is open to speculation.The pyretic effect attained after administration of small doses of GHB, is of interest and suggests rather a neuronal mechanism of action, possibly via interaction with its high affinity binding site.

These results tempt me to hypothesise that administered GHB is, at least in part, a precursor for neuronally active GABA pools which in turn are capable of interacting with both $GABA_A$ and $GABA_B$ receptors. Much of the biochemical data and behavioural correlates can be rationalised by this hypothesis.

DRUGS AND PATHOLOGIC FACTORS WHICH AFFECT THE ENDOGENOUS GHB SYSTEM

Acute administration of ethanol, decreases the GHB content of rat striatum, (141) whereas morphine increases its levels in certain brain regions (158).

Valproate is the most well-known agent that acutely increases cerebral GHB levels (175). This is interesting insofar as this drug antagonises some of the effects of GHB administration which will be the subject of a later section. The mechanism of this increase might be due to inhibition of the mitochondrial enzyme, succinic semialdehyde dehydrogenase (SSADH). In the rat brain, valproate is a competitive inhibitor of SSADH vis à vis SSA with a K_m value of about 0.8 μM. (the author, unpublished results). The SSA level in brain tissue has not been well documented and its concentration of about 0.1 μM as once reported, seems rather low (127). Competitive inhibition of SSADH might be expected to increase the SSA level to a point where reduction of this catabolite to GHB is favoured, because the specific SSA reductase, which is not inhibited by valproate, (150) appears at least, in vitro, to be responsible for SSA reduction to GHB (149). However, recent evidence indicates that an accumulation of GHB would not otherwise affect the functioning of the GABA shunt pathway (25).

The nonspecific cytosolic aldehyde reductase with a high K_m which has been proposed as the enzyme that metabolises GHB to GABA, in vivo (94) is inhibited by valproate (29,95), thus indicating another potential mechanism for elevating the endogenous GHB level. In addition, the mitochondrial monocarboxylic fatty acid oxidising system for which GHB is a substrate in vitro, is also inhibited by valproate (48). Nonetheless, both of these possible metabolic systems require in vitro far higher GHB concentrations than the normal endogenous level, so their significance with regard to the endogenous GHB system is dubious. Valproate may thus block the formation of the GABA pool(s) derived from the administration of GHB.

A mentally and physically retarded patient excreted substantial amounts of GHB and SSA in the urine (89). A number of such cases are now reported, and it is recognised as a rare genetic disease which is caused by a severe lack of SSADH resulting in a considerable build-up of GHB in the serum (137,144). This is most probably produced through the action of specific SSA reductase on the surfeit of the available SSA. The accompanying pathology might be due to the excessive tissue levels of GHB, its reactive aldehyde precursor, SSA, or, GABA metabolically derived from SSA which cannot enter the Krebs cycle. The GABA shunt has been estimated to account for about 10% of the energy flux through the Krebs cycle in brain tissue (7), thus the energy balance could evidently be locally perturbed and this could well be a major factor in the symptomology of the disease.

Post-mortem cerebral tissue from Huntingdon's patients of which the disease is also characterised by neurological disorders (22), contain higher than normal levels of GHB (3) and there is a striatal deficiency of succinate dehydrogenase (185), that is, an enzyme deficiency analogous to that observed in the genetic metabolic disorder referred to above. It could be suggested that a common factor is involved in the aetiology of both diseases. Whether GHB accumulation, and possibly its biotransformation to GABA, is a cause or a symptom of these diseases remains to be elucidated, although valproate has been used with some success to treat some of the symptomology of the metabolic disorder (144). Valproate might block the formation of the GHB-derived GABA pool(s). However, there is a trend towards an inverse relationship between the GABA and GHB levels in Huntingdon's desease (3), and in an animal model of this disease induced by administration of kainic acid (4). As the Krebs cycle should be partially blocked by the lack of succinate dehydrogenase, the biosynthesis of the metabolically active GABA pool might also be inhibited.

The data presented in this section do not in the author's opinion present either positive or negative evidence for a neurotransmitter role for GHB in the CNS. However, they do suggest that malfunctioning of its metabolic pathways may provoke neurotoxic sequelae.

BEHAVIOURAL AND EEG EFFECTS OF GHB OR GBL ADMINISTRATION

The most striking effect is the induction of sedation, sleep and eventually anaesthesia in various animals and man. (Reviewed by Laborit in ref. 102) The major questions in this domain are to what extent this sleep resembles the natural form and how does it compare with that induced by other hypnotics such as the barbiturates, benzodiazepines, and even ethanol. To begin with, the dose of GHB required to induce sleep is considerably greater than that of currently used hypnotic drugs but is far smaller than a hypnotic dose of ethanol. However, in this model, GHB and ethanol display synergy (128) which may indicate that either they act on a common system or that ethanol induces an increase in neuroactive GHB. Such an increase has been documented in the liver (143), although ethanol actually reduces the striatal GHB levels (141).

In rats, the 24h pattern of GBL-induced sleep parallels the normal pattern and is similar to that induced by barbiturates (183). In a human clinical trial, a dose of about 4 mmol /Kg GHB induced sleep which was indistinguishable from natural sleep as determined by behavioural and electroencephalographic criteria (123). In another trial, GHB administration proved to be an excellent hypnotic with few side effects (85). No EEG abnormalities other than those observed with the normal sleep processes are observed (128). However, in cats (208), rats (124), rabbits (155), and monkeys (168), anaesthetic doses of GHB or GBL induced a depressed behavioural state which has been referred to in the rat, as catalepsy (80), and is accompanied by EEG recordings which resemble nonconvulsive epilepsy. Convulsions have been provoked in the cat by tactile stimuli after GHB administration (209). Thus it was suggested that GHB might play a role in the aetiology of absence epilepsy in man (67) despite the huge discrepancies between the normal brain concentrations of this compound and those induced in animals after administration of pro-epileptic doses. However, in at least one experimental animal model, GHB exerts anticonvulsant activity (138), and it attenuates convulsions induced by the administration of a GABA synthesis inhibitor (191). Nevertheless the pro-absence epileptic effects in several species have been proposed and used to serve as animal models of human petit mal epilepsy (167,171), a subject that will be dwelt with in more detail in the next section.

A RESUMÉ AND COMPARISONS OF THE GENETIC, GHB-INDUCED AND $GABA_B$ RECEPTOR-MEDIATED ABSENCE EPILEPSIES

It may be stressed at the outset that the rat model of genetic absence epilepsy (125,202), is exclusively an animal model, but that the EEG and behavioural attributes resemble those observed in human petit mal epilepsy particularly in children. Many data suggest that activation of $GABA_B$ receptors is implicated in this phenomenon (86,91,113,165,184), and that a GTP-binding protein is involved (164). Administration of agonists at the $GABA_B$ site are in some cases proconvulsant (36) whereas antagonists are anticonvulsant (86). Indeed, this receptor has been proposed to play a role in the generation and control of generalised absence epilepsy (113). The petit mal epileptic symptoms induced by peripheral administration of GHB (reviewed in ref. 171) is not applicable to humans (129). In the genetic form of this epilepsy, GHB administration exacerbates the symptoms (43,112) as do general gabamimetic drugs including the $GABA_B$ receptor agonist, baclofen (203), whereas a $GABA_B$ receptor antagonist suppresses the symptoms (113). Similarly, in the GHB model, local application of the $GABA_B$ receptor agonist, baclofen increase the spontaneous epileptic events whereas an antagonist of this receptor suppresses them (168). Intracerebroventricularly applied GABA itself and peripheral administration of an agonist, muscimol of the $GABA_A$-receptor binding sites, prolong the duration of seizures exclusively in young animals (172). As muscimol may be metabolised, it is not certain that it is acting exclusively as a $GABA_A$ receptor agonist in this scenario. Thus, the genetic and GHB-induced models of absence epilepsy are similar and share certain biochemical correlations, one of which may be the result of a common GTP-binding protein mechanism (164).

The biochemical mechanism by which GHB exerts its behavioural effects is not known, but interactions with the binding sites referred to earlier and with the $GABA_B$ receptor are of possible consequence.

FACTORS THAT MODULATE THE BEHAVIOURAL AND EEG EFFECTS OF GHB/GBL ADMINISTRATION: POSSIBLE MODE OF ACTION

The first drugs described that antagonise the EEG effects of GHB administration are some anticonvulsants (66,169) which include valproate that has proven efficacious in the treatment of human petit mal epilepsy. Moreover, it suppresses seizures in the rat genetic absence model referred to above (125). This drug will be the mainstay of this part of the discussion as considerable biochemical data are available concerning its possible mechanisms of action. In this context, valproate inhibits the aldehyde reductase (29,207) which is believed to be responsible for the conversion of GHB to GABA (94,201). In addition, it inhibits the depolarisation-induced release of GHB from rat brain hippocampal slices (195). Thus it would be expected to reduce the GABA pool derived both from endogenous GHB and that derived from its administration. In this context it should be noted that valproate suppresses the visual evoked potentials facilitated by the GABA transaminase inhibitor, γ-vinyl GABA (133) and as such, in this case at least, it could be considered to be acting as an anti-gabaergic drug.

Thus it is tempting to hypothesise that valproate antagonises the behavioural effects of GHB administration via a gabaergic mechanism, possibly via inhibition of the formation of a neuronally active pool of GABA derived from GHB. It could therefore be suggested that the behavioural antagonism induced by valproate administration is due to the reduced levels of GABA derived from GHB. Hence, the initial GHB-induced syndrome might be a result of a gabaergic mechanism. This presupposition is based on the conjecture that at least some of the effects of GHB are due to its metabolism to specialised GABA pool(s). A further argument in its favour is that valproate increases brain GHB levels despite the fact that it antagonises some of the effects caused by its administration.

How can this hypothesis be reconciled with the general view that GABA is a principal inhibitory neurotransmitter in the CNS and hence an increase in the GABA activity would be expected to exert a depressant effect rather than to produce

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