Blockade of the Behavioral Effects of Gamma-hydroxybutyrate by GHB and GABA-B Receptor Antagonists

A.K. Goodwin[1], W. Froestl[2], K.M. Gibson[3], T. Burlingame[3], E.E.W. Jansen[4], C. Jakobs[4], and E.M. Weerts[1]

[1] Division of Behavioral Biology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2] Novartis Pharma AG, Basel Switzerland;
[3]Oregon Health Science University, Portland, OR, USA; [4]Clin. Chem., VU University Medical Center, New Orleans, LA, USA

Introduction

Gamma-hydroxybutyric acid (GHB) is an endogenous substance found in the brain, as well as a drug of abuse. In recent years, GHB has begun to receive more attention due to an increase in reports of non-medical use and a sharp rise in medical emergencies associated with illicit use of GHB.

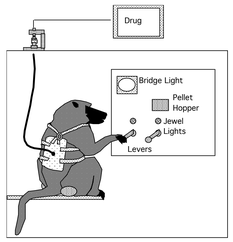
When administered systemically, GHB produces CNS depressant effects that are similar to those produced by classic sedative-hypnotics such as barbiturates and benzodiazepines. GHB also produces a range of adverse effects including agitation, dizziness, nausea/vomiting, seizures, bradycardia, respiratory depression, and unconsciousness. Although once used as an anesthetic, the only therapeutic and legal use of GHB is currently for the treatment of narcolepsy

The neurobiological mechanisms by which GHB produces its behavioral effects are unknown. GHB does not directly modulate GABA-A receptors, which are the primary mechanism for the behavioral actions of both barbiturates and benzodiazepines. GHB binds to two receptor sites in the CNS, the GHB receptor and the GABA-B receptor.

The current study characterized the behavioral effects of acute GHB administration in baboons and evaluated if the GHB antagonist NCS-382 and the GABA-B antagonist CGP36742 would block the behavioral effects of GHB.

Methods

- Four adult male baboons (*Papio anubis*) with chronic indwelling intragastric (IG) catheters
- Catheters were protected by a vest/ tether system that permitted free movement within the cage
- Distilled water (450 mls/day) was infused continuously via a peristaltic pump to maintain catheter patency
- The home cage served as the experimental cage and was equipped with an intelligence panel containing a Lindsley lever, a speaker, stimulus lights and a food hopper for the experimental control of behavior
- Sessions were controlled remotely by PCs with MED Associates Software and hardware



Experiment 1: Effects Of GHB alone

- 150 mls of GHB or water (VEH) administered as a bolus infusion
- FR schedule of pellet delivery during daily 20-hr sessions beginning 60-min after drug administration
- Frequency and duration of 21 behaviors and 8 postures observed during 60 min periods beginning 60-min after drug or VEH infusion
- Fine motor task presented immediately before and again after the 60-min observation period.

Experiment 1: Results

Table 1. Number of subjects showing behavioral signs of sedation, muscle relaxation and abdominal discomfort after GHB administration

	GH ose (mg/kg)				
	00 (n=4)	180 (n=4)	240 (n=4)	320 (n=4)	420 (n=3*)
Resting Postures	1	2	3	4	3
Lip droop	0	1	1	3	2
Ataxia	0	1	1	3	2
Defecation w th Diar hea	0	0	2	2	2*
Vomit ng	0	0	1	2	2*
Head Low r Posture	1	0	2	3	2
Tremor Je ks	0	0	0	0	2

*Baboon KH projec ile vomiting and diarrhea within 20 min af er do ing-no ob er ation

Figure 1. Effects of GHB on food-maintained behavior

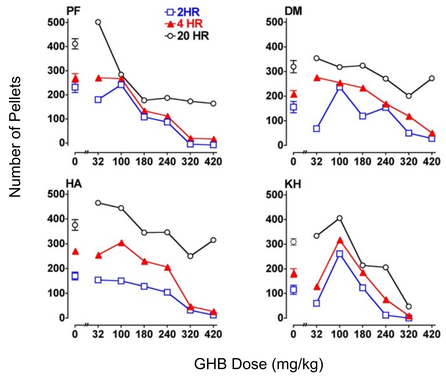


Figure 2. Effects of GHB on fine motor task

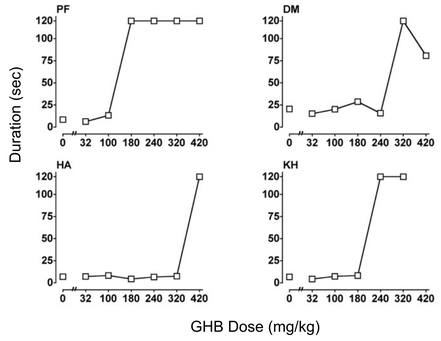
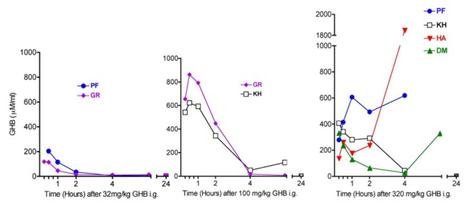


Figure 3. GHB in blood



Experiment 2: Effects of GABA-B and GHB antagonists on the behavioral effects of GHB

- NCS-382 (0.1-3.2 mg/kg), CGP36742 (10-56 mg/kg), or VEH (sterile water) injected IM immediately prior to IG infusion of 320 mg/kg GHB or VEH
- All other procedures the same as Experiment 1

Experiment 2: Results

Table 2. Number of subjects showing behavioral signs of sedation, muscle relaxation and abdominal discomfort after antagonists + GHB administration

Dose (mg kg)	320 GHB AL NE		320 GHB + 10 CGP	320 GHB + 32 CGP	320 GHB + 56 CGP
P stures	4		0	1	0
Lip droo	3		0	0	0
Ataxia	3		0	1#	0
Defecatio with Diarrhea	2		0	0	0
V mitin	2		1	0	1$
Head Lower P sture	3		0	0	0
Tremor Jerk	0		0	0	0

320 GHB + 1 NCS (n=4)	320 GHB + 32 NC (n=4)	320 GHB +1 NCS (n=3)	320 GHB +3.2 CS (n=4)
0	1	1	0
0	1	1	2
0	2	2	1
1	1	1	1
2	2	1	2
0	0	1	1
0	1	1	0

Figure 4. Effects of NCS-382pretreatment on food-maintained behavior

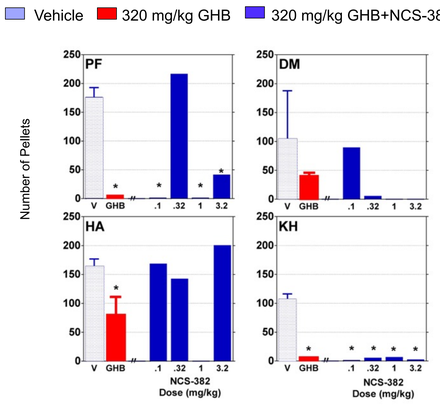


Figure 5. Effects of CGP36742 pretreatment on food-maintained behavior

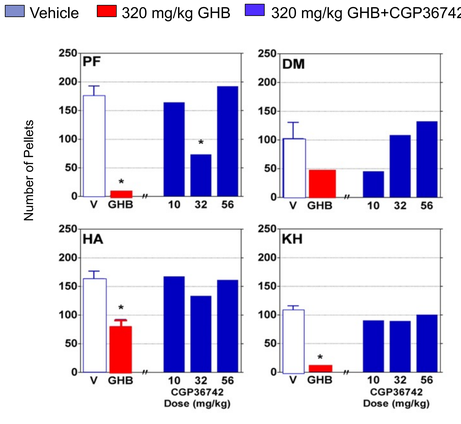


Figure 6. Effects of NCS-382 pretreatment on the fine motor task

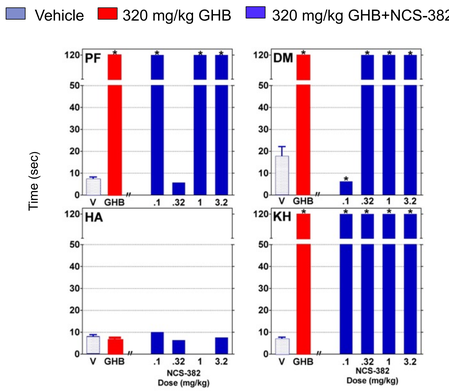
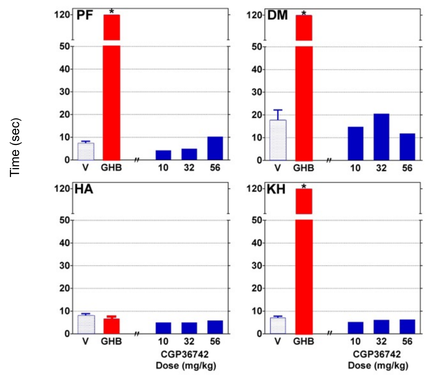


Figure 7. Effects of CGP36742 pretreatment on the fine motor task



Summary and Conclusions

- GHB dose-dependently reduced food-maintained behavior and disrupted performance on the fine motor task. Pre-treatment with a GABA-B antagonist restored food-maintained behavior to vehicle levels, while pre-treatment with a GHB receptor antagonist produced inconsistent effects.
- While GHB may share some behavioral effects with classic sedative hypnotics, the behavioral pharmacology of GHB is distinctly different
- These data are consistent with reports the GABA-B receptor plays an important role in the behavioral effects of acute doses of GHB
- The role of GHB receptors in mediating the behavioral effects of exogenously administered GHB remain unclear

Acknowledgements

- Supported by NIH/NIDA R01-DA14919 (Weerts)
- GHB and NCS-382 were provided by NIDA drug Supply program; CGP36742 was provided by Novartis Pharma