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GAMMA-HYDROXYBUTYRATE (GHB)-DEFICIENCY IN ALCOHOL-DEPENDENCE?

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I wish to propose a hypothesis that could help explain some of the effects of baclofen in alcohol dependence that are described in Dr. Bucknam's case study (Bucknam, 2007) and in my self-case report (Ameisen, 2005). At a behavioural level, alcohol, baclofen and GHB all share sedative/hypnotic effects in humans. Clinical trials have shown baclofen to reduce anxiety in alcoholic (Krupitsky *et al*., 1993; Addolorato *et al*., 2002) and non-alcoholic (Breslow *et al*., 1989; Drake *et al*., 2003) patients alike. And somnolence is an overwhelmingly prevalent side effect of baclofen. Yet unlike other sedative/hypnotics (benzodiazepines, meprobamate, barbiturates), baclofen and GHB have been specifically shown to reduce craving in alcoholic patients (Addolorato *et al*., 2002; Caputo *et al*., 2003; Nava *et al*., 2006). In animals, effects of baclofen on anxiety are more heterogeneous. While some studies demonstrate that baclofen has sedative activity (Carai *et al*., 2004), lack of anxiolytic activity (Dalvi and Rodgers, 1996) and even anxiogenic actions (Car and Wisniewska, 2006) have also been reported. Also, while there are reports showing baclofen to increase severity of alcohol withdrawal in animals (Humeniuk *et al*., 1994), the efficacy of baclofen in the treatment of acute withdrawal syndrome has been shown to be comparable to that of diazepam in clinical trials (Addolorato *et al*., 2006). In mice, Carai *et al* established that the sedative/hypnotic effect of GHB is, like that of baclofen, mediated by the stimulation of GABA(B) receptors (Carai *et al*., 2001) which adds support to the hypothesis that the GABA(B) receptor constitutes a central site of action of GHB. Functionally, both baclofen and GHB increase a potassium current and decrease the H-current in hippocampal neurons via GABA(B) receptor (Schweitzer *et al*., 2004). Of alcohol, GHB and baclofen, only one is a naturally occurring molecule: GHB. This leads me to raise the hypothesis that a primary dysfunction in GHB, such as a quantitative or functional deficit, could be partly responsible for the dysphoric syndrome (anxiety, insomnia, muscular tension. . .) that precedes and later coexists with alcohol dependence. And that baclofen effect could compensate for some of the deficit of GABA(B)-mediated effect of GHB, and suppress dysphoria and dependence. Most sedative/hypnotics can cause dependence. In clinical practice, of these two agents that stimulate GABA(B) receptors, GHB causes dependence, while dependence has not been reported with baclofen. This could be related to GHB's many sites of action aside from GABA(B). Animal studies should be performed to test this hypothesis. Of interest, a GHB receptor has recently characterized in the human brain.

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