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Effect of gamma-butyrolactone and baclofen on plasma prolactin in male rats*

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Gamma-hydroxybutyrate (GHB), which occurs as a natural metabolite in mammalian brain [1], or its precursor gamma-butyrolactone (GBL), given systemically, can increase dopamine levels in the neostriatum without affecting norepinephrine or serotonin levels [2]. GHB or GBL does not inhibit monoamine oxidase or catechol-*o*-methyltransferase indicating that the increase in dopamine is not due to interference with its metabolism [2]. GHB causes a marked decrease in the utilization of dopamine [3]. Unit recordings of dopamine neurons in the zona compacta of the substantia nigra indicate that GHB administered systemically decreases the firing of these neurons [4]. These studies are consistent with the thesis that GHB inhibits impulse flow in dopamine neurons in the neostriatum [5].

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It has been proposed that the effect of GHB on dopamine neurons may be due to a direct or indirect stimulation of an inhibitory gamma-aminobutyric acid (GABA) mechanism in the substantia nigra [6].

Dopaminergic neurons of the tuberoinfundibular region of the hypothalamus inhibit prolactin release from the anterior pituitary by a direct inhibitory effect of dopamine on the pituitary [7] or by promoting the release of prolactin inhibitory factor [8], or by both mechanisms. Drugs such as dopamine receptor blockers, e.g. chlorpromazine, which decrease the dopaminergic influence on the pituitary, increase plasma prolactin [9]. Alpha-methylparatyrosine (AMPT) which inhibits the synthesis of dopamine also increases plasma prolactin [10]. Intraventricular injection of GABA raises prolactin on the morning of proestrous in intact female rats and in ovariectomized rats [11].

We were interested in determining if GHB inhibited impulse flow in the dopaminergic neurons of the hypothalamus and thereby increased plasma prolactin. We report

Table 1. Effect of drugs on rat plasma prolactin*

	Dose (mg/kg)	Duration	Plasma prolactin† (ng/ml)	*P*
Saline		30 min	10.4 ± 3.6	
Gamma-hydroxybutyrolactone	200	30 min	10.8 ± 4.5	NS‡
	400	30 min	14.4 ± 3.6	NS
	750	30 min	42.4 ± 14.6	<0.01
	1500	30 min	61.7 ± 14.6	<0.01
Baclofen	20	1 hr	9.7 ± 2.5	NS
	25	1 hr	47.2 ± 23.4	<0.01
	50	1 hr	57.6 ± 21.7	<0.01
Alpha-methylparatyrosine-methyl ester	125 × 2	4, 24 hr	33.8 ± 7.7	<0.01
Trifluoperazine	2.5	1 hr	68.4 ± 12.7	<0.01

* All groups consisted of five male rats.
† Mean ± S. D.
‡ Not significant.

here that GBL does raise plasma prolactin in male rats. We also found that baclofen (β-[4-chlorophenyl]-α-aminobutyric acid), a putative GABA agonist [12], also increases rat plasma prolactin levels.

Male Sprague Dawley rats weighing 175–200 g were used in this study. GBL, baclofen, trifluoperazine and AMPT-methyl ester were injected intraperitoneally. (AMPT-methyl ester was injected in two equal doses 24 and 4 hr prior to sacrifice.) Rats were sacrificed at the time indicated in Table 1. Rats were anesthetized with ketamine prior to obtaining heparinized blood from the inferior vena cava. Ketamine does not affect plasma prolactin in rats [13]. Its use contributed to smaller variances in plasma prolactin levels than guillotining rats. The methods used to determine rat prolactin have been described elsewhere [14]. The prolactin standard utilized was NIAMDD rat-PRL-RP-1. The significance of the difference in mean prolactin levels between drug-treated animals and controls was determined by means of a one-way analysis of variance. The differences between groups was tested by means of the Honestly Significant Difference test of Tukey [see ref. 15].

As can be seen in Table 1, GBL in doses of 750 and 1500 mg/kg raised male rat prolactin levels at 30 min. Doses of 200 and 400 mg/kg had no effect despite the fact that GBL at 200 mg/kg has been reported to inhibit the activity of 50 per cent of A9 neurons [4]. There is a suggestion that plasma prolactin increased further as the dose of GBL was raised from 750 to 1500 mg/kg. Baclofen increased plasma prolactin at doses of 25 and 50 mg/kg but not at 10 mg/kg. The increase in plasma prolactin produced by GBL and baclofen was comparable to that produced by the neuroleptic, trifluoperazine, and was somewhat larger than that produced by AMPT-methyl ester (Table 1).

GBL and baclofen, though both have been thought of as GABA agonists [6, 12], and though intraventricular GABA can elevate serum prolactin in rats [11], may augment prolactin secretion by other than a gabergic mechanism. The GABA agonistic properties of baclofen have been challenged [16] and those of GHB are far from certain. The inhibition of impulse flow in dopamine neurons by GHB may occur other than via a GABA agonist mechanism [4].

A direct inhibition of the release of dopamine from tuberoinfundibular neurons by GHB would be expected to increase plasma prolactin levels [9]. However, the fact that 200 and 400 mg/kg of GBL did not increase plasma prolactin, though both doses have been shown to inhibit impulse flow in A9 dopamine neurons [4], argues against inhibition of impulse flow as the mechanism for augmentation of prolactin secretion, but it is possible that the hypothalamic dopamine neurons are more resistant to the effects of GHB.

It is possible that the effect of GHB on plasma prolactin is a non-specific anesthetic effect. Ether and barbiturates produce prolonged increases in plasma prolactin, while urethane and chloral hydrate produce transient increases (peak at 10 min, no increase by 30 min [13]). However, ketamine, as previously mentioned, produces no increase in serum prolactin levels, at anesthetic doses [13].

It is unlikely that the increase in plasma prolactin produced by GBL is brought about by promoting a direct serotonergic influence on plasma prolactin [17] since GBL, 600 mg/kg, had a minimal effect on the firing rate of dopamine neurons [4]. An indirect effect of serotonin release is not ruled out.

Since endogenous levels in GHB in rat brain are so low [1], it seems unlikely that GHB could play any significant effect in regulating prolactin secretion. It has been proposed that GABA does play such a role [11].

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