Do β adrenergic agents directly stimulate gastrin secretion?

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Summary. Isoproterenol if given during methacholine stimulation in dogs neither depresses gastric secretion nor elevates serum gastrin. Therefore, we conclude that β adrenergics (isoproterenol) are unlikely to be direct liberators of gastrin, but raise serum gastrin indirectly only if they inhibit gastric secretion.

It has been suggested that β adrenergic agents stimulate the release of gastrin from the pyloric G cells because administration of epinephrine raised serum gastrin in anesthetized dogs[2]. Phenoxybenzamine was found to depress the elevated serum gastrin seen in patients with pheochromocytoma[2].

Another explanation for this suggested itself to us based on the fact that many agents and procedures which depress gastrin stimulated gastric secretion also elevate serum gastrin. The extreme example of this is the elevated serum gastrin in achlorhydria[3]. Our hypothesis is that the depressed parietal cell itself signals the G cell to produce more gastrin. Isoproterenol does depress gastrin stimulated secretion, and propranolol inhibits the decrease, however, isoproterenol does not depress cholinergically stimulated gastric secretion[4]. If isoproterenol causes liberation of gastrin, serum levels should rise whether isoproterenol is administered, alone, with gastrin or with methacholine. If gastrin levels do not rise when isoproterenol is given with methacholine this then is an argument in favour of the notion that the increase in serum gastrin is a consequence of inhibition of fundic secretion.

Methods. In 4 fasted, conscious dogs, with Heidenhain pouches, innervated pyloric pouches and gastric fistulae, methacholine was administered i.v. at 4 µg/min for 1 h. Then isoproterenol was added at 0.25 µg/min for a further h. Collections were at 10 min intervals. The last 3 collections of each period were used for calculating group means and paired t. Pouch secretion was collected by the washout method, pepsin was determined by Anson[5] technique and gastrin by Cataland et al.[6] method.

Results. It will be noted from the table that gastrin levels in control experiments with methacholine are not significantly different from those with added isoproterenol. The dose of isoproterenol used invariably produced a marked depression in pentagastrin stimulated secretion, but not (see table) in cholinergically promoted secretion.

	Pouch		Fistula		
	H^+ mEq	Pepsin units	H^+ mEq	Pepsin units	Gastrin µg/ml
Control methacholine	0.2871 ± 0.0662	115.59 ± 11.65	1.1861 ± 0.4366	415.6 ± 169.5	22.25 ± 1.493
Methacholine plus isoproterenol	0.2766 ± 0.0533	90.56 ± 25.17	1.6421 ± 0.6946	341.5 ± 142.2	28.50 ± 3.775

Each figure group mean of 4 experiments in 4 dogs ± SE.

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Profound hypothermia in golden hamsters *(Mesocricetus auratus)* induced by serotonergic potentiating and noradrenergic inhibiting drugs

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Summary. Profound hypothermia (6 °C) was induced in cold exposed golden hamsters *(Mesocricetus auratus)* by a combination of drugs that potentiate brain serotonergic activity (fluoxetine and pargyline) and inhibit noradrenergic activity (alpha-methyl-p-tyrosine). Individual drugs and combinations of 2 were ineffective.

Serotonin and norepinephrine are neurotransmitters involved in temperature regulation[2-5]. Drugs that influence serotonin and norepinephrine synthesis or activity modify body temperature by as much as 6 °C. These drugs include p-chlorophenylalanine (PCPA), an inhibitor of serotonin synthesis; fluoxetine, a potentiator of serotonergic activity; alpha-methyl-p-tyrosine (α-MPT), an inhibitor of norepinephrine synthesis; pargyline, a potentiator of both serotonin and norepinephrine. Inhibition of serotonin synthesis with PCPA elevated the body temperature of rats[6,7], whereas enhancement of serotonergic activity by fluoxetine[8] or pargyline[9] lowered the temperature. Inhibition of norepinephrine synthesis with α-MPT also slightly lowered body temperature of rats[10]. Because serotonergic and noradrenergic mechanisms may have antagonistic effects, drug-induced alteration in one might be compensated by the other, thereby limiting the hypothermia. Therefore, drugs that simultaneously stimulate serotonergic and inhibit noradrenergic mechanisms should produce a deep hypothermia (figure).

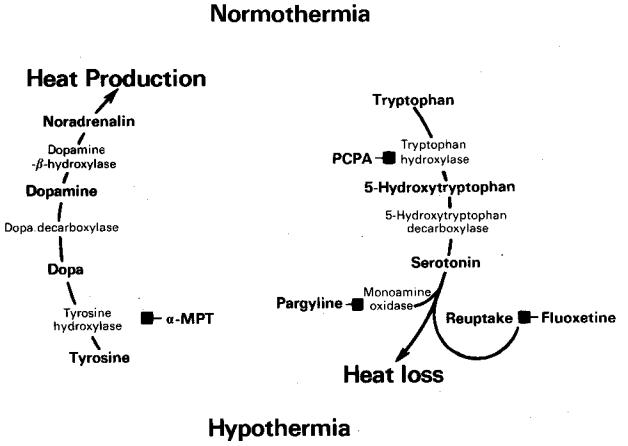
Adult golden hamsters, *Mesocricetus auratus* (100-150 g b. wt) of mixed sexes, were maintained on a 10-h daily photoperiod (07.00-17.00 h). From March 15 to May 16, 1977, on various dates, a total of 73 hamsters were injected i.p. at 13.00 h with one or more of the following drugs: 10 mg α-MPT (Sigma Chemical Company, St. Louis) in 0.2 ml, 8 mg pargyline (Sigma) in 0.2 ml, 5 mg fluoxetine (Lilly Research Laboratories, Indianapolis) in 0.5 ml, and

100 mg PCPA (Sigma) in 0.5 ml, of 0.85% saline. The treatments (and numbers) were as follows: saline (8); α-MPT (4); pargyline (4); fluoxetine (4); α-MPT and pargyline (4); α-MPT, and fluoxetine (4); pargyline and fluoxetine (4); α-MPT, pargyline, and fluoxetine (29). PCPA pre-treatment (3 days at 1000) and then α-MPT, pargyline, and fluoxetine (12). The injected hamsters were placed in a cold room (6 °C). The animals were observed every 3 or 4 h and those remaining normothermic were injected again the next day. Esophageal temperatures were determined with a telethermometer equipped with a thermistor probe.

The combination of α-MPT, pargyline, and fluoxetine produced a profound hypothermia (table). Two-thirds of the animals responded the next day following the injections. In responding hamsters (27 out of 29) the body temperature declined to the ambient temperature (6 °C) within 6–10 h. During profound hypothermia at 6 °C there were no visible respiratory movements, the paws and nose were bright pink, and there was a slight trembling of the front feet. A further reduction of ambient temperature to 0 °C killed the several hamsters tested. After a return to room temperature (22 °C) for about 2 h those hamsters exposed to no lower than 6 °C ambient temperature became active. Their temperatures remained slightly depressed for 1 or 2 days. Hamsters kept in profound hypothermia longer than 4–10 h died. Neither individual drugs nor combinations of 2 of the 3 drugs (α-MPT, pargyline, and fluoxetine) induced profound hypothermia.

In order to test the duration of the drug-induced effects, 4 days after drug-induced hypothermia and rewarming, 4 hamsters were returned to the cold room. After 2 days only 1 hamster reentered a deep hypothermia (12 °C). Additionally, serotonin synthesis was evidently necessary for the development of drug-induced hypothermia inasmuch as PCPA (a serotonin synthesis inhibitor) pretreatment prevented profound hypothermia in 10 of 12 hamsters injected with α-MPT, pargyline, and fluoxetine.

In the natural hypothermia of hibernation both serotonergic and noradrenergic adjustments have been reported. High seasonal levels of brain serotonin occur during hibernation in the European hedgehog, *Erinaceus europaeus*[11], and the pale bat, *Antrozous pallidus*[12]. High levels of brain serotonin are correlated with the ability to hibernate in the golden-mantled ground squirrel, *Citellus lateralis*, and the round tailed ground squirrel, *Citellus terreticaudus*[13]. Furthermore, arousal from hibernation is delayed by injections of serotonin or its precursor 5-hydroxytryptophan in the suslik, *Citellus erythrogenys major*[14,15], and by injections of α-MPT in the golden hamster, *Mesocricetus auratus*[16]. On the other hand, a precursor of norepinephrine, L-dopa, arouses hibernating European hedgehogs[11].



Serotonergic and noradrenergic pathways in thermoregulation.

Profound hypothermia induced by drugs*

Drug treatment	Number	Responsive**	Nonresponsive
Saline	8	0	8
α-MPT	4	0	4
Pargyline	4	0	4
Fluoxetine	4	0	4
α-MPT, pargyline	4	0	4
α-MPT, fluoxetine	4	0	4
Pargyline, fluoxetine	4	0	4
α-MPT, pargyline, fluoxetine	29	27	2
PCPA, α-MPT, pargyline, fluoxetine	12	2	10

*Hamsters were subjected to 6 °C following injections of drugs. **6–10 °C body temperature after 1 or 2 daily injections.

The golden hamster may hibernate after prolonged cold exposure[17], but to conclude that profound hypothermia induced by α-MPT, pargyline, and fluoxetine is equivalent to the natural hypothermia of hibernation would be premature. Perhaps manipulation of dose and frequency of drug administration would prolong hypothermia. Such findings would support the hypothesis that hibernation depends on active serotonergic neural pathways and relatively inactive noradrenergic pathways. As a practical note, heart and brain surgery often require hypothermia and present techniques of inducing hypothermia in man involve extraordinary skill, knowledge, and vigilance[18]. Thus, the drugs employed in the present study to produce a profound hypothermia may have possible clinical applications.

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