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α_2 AGONIST-INDUCED EFFECTS ON GROWTH IN RATS

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In mice, chronic administration of the α_2-agonist guanfacine resulted in decreased metabolic rate accompanied by decreased liveweight gain and, perhaps surprisingly, inferior metabolic efficiency (Sillence et al. 1990). We concluded from this work that the catabolic effects of guanfacine could be due to changes in the activity of secondary hormones. Two experiments using rats to investigate possible causes of the observed catabolism are reported here.

In both experiments, individually-housed ad lib-fed female Wistar rats (approximately eight weeks old) received daily subcutaneous injections of either guanfacine (0.5 mg/kg), or vehicle. In Experiment one, no significant difference was observed in live-weight gain, or in indicators of metabolic efficiency (e.g. feed conversion ratio). However, a hind limb muscle bundle (gastrocnemius, soleus, and plantaris), selected as an index of skeletal muscle growth, was significantly lighter in guanfacine-treated animals than in controls. This could be explained by an increase in corticosterone secretion, and indeed assays revealed a significant increase in the plasma concentrations of this catabolic hormone (accompanied by a predictable elevation in plasma glucose levels) in treated animals from both experiments.

In Experiment two, significantly reduced growth again illustrated the catabolic effect of guanfacine. Analysis of glucose from daily urine samples showed a large and immediate increase with guanfacine treatment. Interestingly, this parameter apparently mimics the changes we have observed in metabolic rate in mice (data not presented), where values for treated animals approach control values with time. Such changes could indicate development of tolerance to the α_2-agonist treatment, perhaps through down-regulation of the associated receptors, and that α_2-receptors might directly or indirectly mediate both effects.

Parameter		Control	Guanfacine	P	Experiment	n
Muscle bundle (g)		2.92	2.72	<0.01	1	10
Live-weight gain (g)		27.7	20.2	<0.05	2	12
Plasma corticosterone (nmol/l)		248	652	<0.05	2	12
Plasma glucose (mmol/l)		7.68	9.33	<0.001	2	12
Urinary glucose (mg/day)	Day 1	0.79	34.80	<0.001	2	12
	Day 6	0.60	6.95	<0.05	2	12

We conclude that the catabolic effects of guanfacine observed in rodents may be related to the secondary effect of increased secretion of the catabolic adrenal hormone, corticosterone. Planned studies of α_2-receptor densities and potential sources of energy loss may further clarify the mechanisms involved.

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