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Dopamine receptor modulation of corticosterone secretion in neonatal and adult rats

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Abstract—The effects of the dopamine agonist, pergolide, upon plasma corticosterone levels have been studied in 30 day old neonatal and adult rats. Dose-related elevations in corticosterone were observed at both ages and these elevations were blocked by the dopamine (D2) receptor antagonist spiperone. These studies demonstrate that dopaminergic neurochemical control of the hypothalamus-pituitary-adrenal axis exists in four week old rats in contrast to our previous studies which have shown opioid control to be absent at this age. It appears that neurochemical control of corticosterone is dissimilar in the neonate.

It is well recognized that the adrenal cortex of the rat is relatively immature in the first week after birth. Though some studies have reported elevations of corticosterone before the second postnatal week (Walker et al 1986) most reports indicate that adrenal cortex responses to stress do not appear until the third week of life (Haltmeyer et al 1966; Bailey & Kitchen 1987).

There are several neurochemical inputs in the control of the adrenal cortex and most appear to be manifested at the hypothalamic level; these include noradrenaline, acetylcholine, dopamine, 5-hydroxytryptamine, γ-aminobutyric acid and opioid peptides and the evidence for their involvement comes primarily from studies in adult animals (for review see Tuomisto & Mannisto 1985). We have recently reported (Bailey & Kitchen 1987) that several opioid agonists which modulate corticosterone levels in the adult rat are without effect in the postnatal period up to day 45. This has raised the question as to whether the neurochemical control of corticosterone responses to stress is different in young animals. We report here studies with a dopamine receptor agonist, pergolide, for modulating effects on corticosterone in postnatal and adult rats.

Materials and methods

Wistar albino rats (University of Surrey strain) of either sex were maintained under constant conditions as previously described (Bailey & Kitchen 1987). All experimental manipulations were carried out between 0730 and 0930 h. Measurements of plasma corticosterone were made in 30 day old neonates and adult rats (> 60 days; 200–250 g). Basal and vehicle-injected controls were run in parallel with drug administration and mean determinations represent measurements made on at least two separate days to avoid inter-day variability.

Pergolide mesylate was a gift from Eli Lilly (Indianapolis, USA) and spiperone, a gift from Janssen Pharmaceuticals (Wantage, UK). Pergolide and spiperone were dissolved in 0·9% NaCl/0·2% citric acid and brought to pH 5·0 with sodium hydroxide. Pergolide and spiperone were injected intraperitoneally in a volume of 0·15–0·2 mL and concentrations are expressed as salts. Pergolide was injected 1 h before the animals were killed and, when studied, spiperone was given 1 hr before the pergolide administration. Appropriate vehicle-injected controls were included in all experiments. Rats were killed by decapitation and trunk blood was collected into heparinized tubes. Plasma corticosterone was determined fluorimetrically as described previously (Kitchen & Rowan 1984) and duplicate assays were carried out for standards and samples.

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Results

Injections of saline or drug vehicles did not significantly alter plasma corticosterone levels when measured 1 h after administration in either 30 day old or adult animals. Pergolide caused a marked dose-related elevation in plasma corticosterone in both 30 day and adult rats (Fig. 1). At the highest dose (1 mg kg^{-1}) corticosterone levels were equivalent at the two ages. Elevations in corticosterone induced by 0·3 mg kg^{-1} pergolide were completely antagonized by spiperone at 0·3 mg kg^{-1} in both adult and 30 day old rats (Fig. 2). A lower dose of spiperone (0·03 mg kg^{-1}) showed no antagonism of pergolide-induced elevations in corticosterone in adult animals (pergolide 0·3 mg kg^{-1}: 62·9 ± 3·9; spiperone 0·03 mg kg^{-1} + pergolide 0·3 mg kg^{-1}: 57·0 ± 7·1; spiperone 0·03 mg kg^{-1}: 27·2 ± 5·0 μg/100 mL: n > 6).

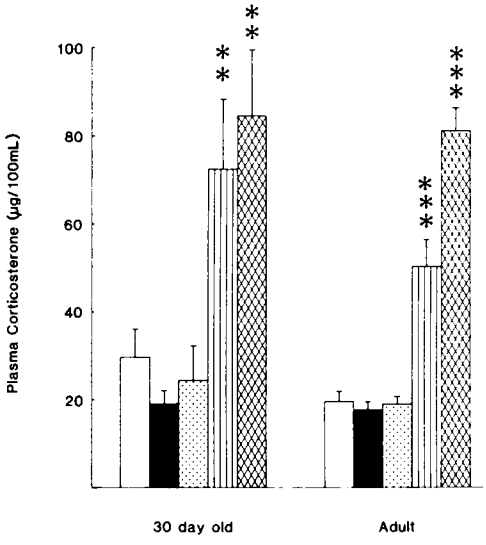

FIG. 1. Effects of acute pergolide administration on plasma corticosterone levels in neonate and adult rats. Each column shows the mean of at least 4 observations and vertical lines indicate s.e.m. Open columns: naive; closed columns: vehicle treated; dotted columns: pergolide 0·05 mg kg^{-1}; barred columns: pergolide 0·2 mg kg^{-1}; cross-hatched columns: pergolide 1 mg kg^{-1}. *t*-test vs vehicle $^{**}P < 0.01$, $^{***}P < 0.001$.

Discussion

The dopamine agonist pergolide caused elevations in corticosterone equivalent to those reported by Fuller & Snoddy (1981) in adult animals. Pergolide was also effective in elevating corticosterone in 30 day old rats in contrast to our observations

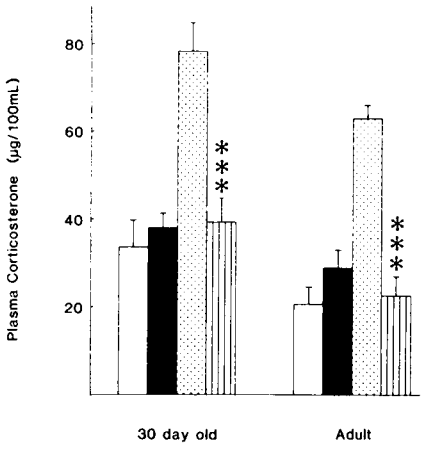

FIG. 2. Spiperone antagonism of pergolide induced elevations in plasma corticosterone levels in neonate and adult rats. Each column shows the mean of at least 6 observations and vertical lines indicate s.e.m. Open columns: vehicle-treated; closed columns: spiperone 0·3 mg kg^{-1}; dotted columns: pergolide 0·3 mg kg^{-1}; barred columns: spiperone 0·3 mg kg^{-1} + pergolide 0·3 mg kg^{-1}. *t*-test; pergolide vs spiperone + pergolide $^{***}P < 0{\cdot}001$.

with opioid receptor agonists which are ineffective at this age (Bailey & Kitchen 1987). That the pergolide effects were dopamine receptor mediated in both neonates and adults was confirmed by antagonism of pergolide effects with spiperone at doses shown by others to be selective at dopamine receptors (Fuller & Snoddy 1981, 1984), the doses of spiperone required to block 5-hydroxytryptamine receptors involved in corticosterone secretion being 10-fold higher than used in our study (Fuller & Snoddy, 1981).

The ontogenetic development of both dopamine and dopamine receptors occurs postnatally and is complete by the fourth postnatal week in the rat (Murrin & Zeng 1986; Nomura et al 1976). This developmental profile is essentially similar to that reported for opioid peptides and opioid receptors (Bailey & Kitchen 1985; McDowell & Kitchen 1986) and yet the control of corticosterone is clearly dissimilar. The lack of effect of opioids upon corticosterone in 30 day old rats (Bailey & Kitchen 1987) cannot therefore be attributed to neuronal or postsynaptic receptor immaturity. Whether other neurochemical systems are active in the neonate is currently under investigation; but differences in the control of corticosterone in neonates might be a biologically protective function.

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