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THE EFFICACY AND MECHANISM OF ACTION OF ANABOLIC AGENTS AS GROWTH PROMOTERS IN FARM ANIMALS

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SUMMARY

Anabolic agents are substances with physiological functions similar to those of the sex steroids which increase nitrogen retention and protein deposition in farm animals. When used correctly they significantly increased the daily live-weight gain and food conversion efficiency (FCE) in cattle and sheep but were less effective in pigs and poultry. A hypothesis to explain the role of sex steroids in the growth rate of cattle suggested that both androgens and oestrogens were necessary to realise the maximum growth rate. Thus in practice the best responses in growth rate and also FCE were observed when androgens were used in females and androgens combined with oestrogens were administered to steers. The mechanism of action of anabolic agents is not fully understood. The actions of androgens and oestrogens may be different. There is the possibility that androgens may have a direct action on the muscle cell. Oestrogens, but not androgens, may act indirectly through the regulation of the concentration of growth hormone and insulin in the plasma. Evidence is also presented to show that both androgens and oestrogens depress the concentrations of thyroid hormones in the plasma of cattle and sheep and this effect may be associated with their mechanism of action.

The use of anabolic agents in farm animals can increase the efficiency of meat production. This benefit in treated animals results in an increased live-weight gain, an improvement in feed conversion efficiency (FCE) and often an improvement in carcase quality. The use of anabolic agents is practised world-wide and most countries consider that the benefits of these compounds outweight their risks to public health.

The majority of anabolic agents have functional properties similar to those of the sex steroids, the androgens, oestrogens and progestins, and it was the development of some derivatives of stilbene as cheap synthetic oestrogens which resulted in the use of these compounds for growth promotion from 1950 onwards. However, the potential health hazards associated with the use of some stilbene derivatives, especially diethylstilboestrol (DES), were recognised and during the 1970s several countries banned the use of these drugs. This resulted in an intensive search by industry for alternatives, and although the cost of production of natural steroids like testosterone, oestradiol and progesterone is economic, several new synthetic steroids like trenbolone acetate and melengesterol acetate have also been developed. Another compound, zeranol, a resorcyclic acid lactone with oestrogen-like activity is also widely used. Figure 1 shows the names and formulae of the most commonly used anabolic agents in farm animals.

GROWTH PROMOTION IN THE YOUNG ANIMAL

Hormones regulate growth in animals from conception to death. The earliest effects of androgens are the differentiation of the foetus into the male form. Normally the production of androgens is genetically controlled by the foetus but somewhat similar effects of masculinisation of foetuses can occur if androgens are administered during pregnancy [1]. Growth rates of neonatal rats were increased following administration of androgens and also ovariectomy [2–4]. Thus it may be possible in the future to improve the growth rate of females by androgen manipulation of the foetus or neonate: this could create an animal which would have growth factors similar to those of a male. In practice exogenous hormones are administered a few months after birth to veal calves, wether lambs, pigs, turkeys and fish. Veal calves have received much attention and the exhaustive studies of Van der Wal and his co-workers [5] have shown beyond doubt that anabolic agents greatly increase live-weight gain and FCE. However, in all species and sexes of animals the choice of the best agent is important to obtain maximum benefit. Table 1 shows the benefits in veal calves administered different anabolic agents. The greatest benefits were seen in animals receiving an androgen, with a high myotropic index, combined with an oestrogen.

Lambs

In young sheep the main use of anabolic agents is in finishing wether lambs (castrate males). Studies in France [7] suggested that combined preparations of androgen and oestrogen improved the growth rate and increased FCE in wether lambs compared with controls. The oestrogens, zeranol and hexoestrol are reported to show some improvements in growth rate and FCE but the responses and economic returns are not sufficient to encourage wide scale use [8].

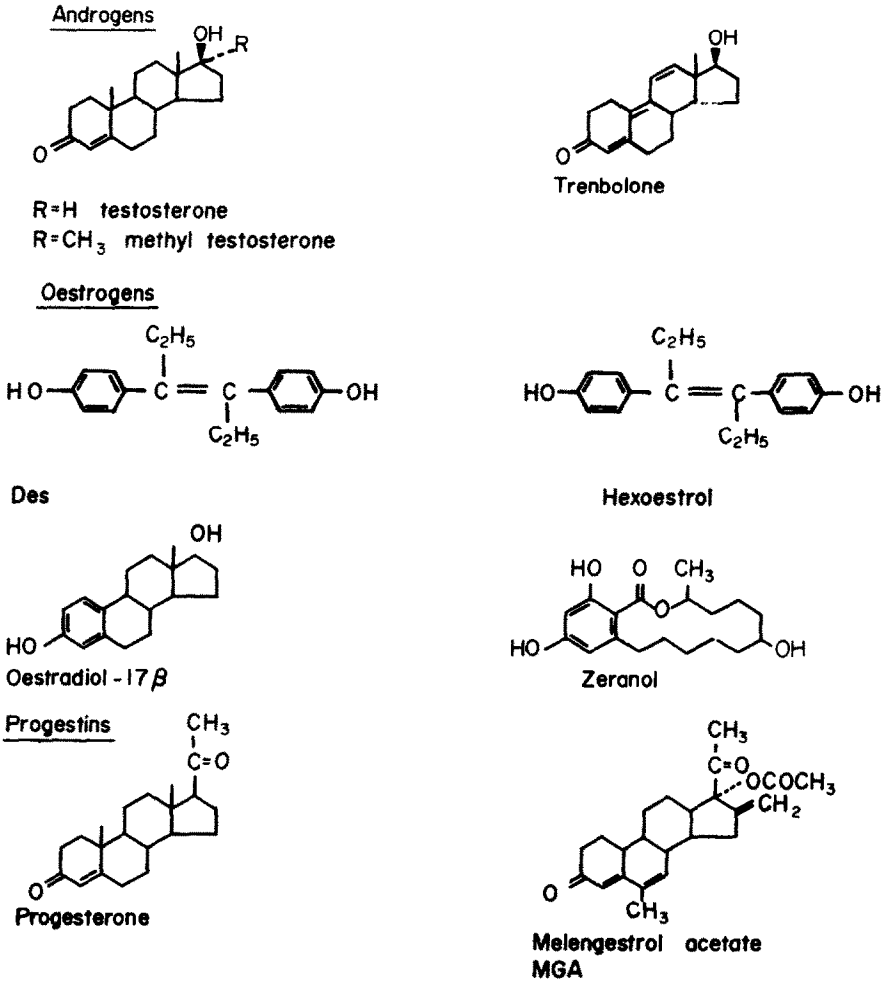

Fig. 1. Anabolic agents used in farm animal production

Pigs

The effect of anabolic agents in young pigs is slightly different from that in cattle or sheep. The principle effect in pigs is an increase in the lean:fat tissue ratio. Backfat thickness is reduced in treated animals and carcase quality improved in favour of larger hams and loins [9]. In the same study improvements were observed in live-weight gain, FCE and nitrogen retention in castrate male pigs receiving either implants of trenbolone acetate and oestradiol or oral administration of trenbolone acetate plus ethnyl oestradiol. In farm practice implants are not yet

Table 1. Effects of anabolic agents on the performance of veal calves

Treatment	Dose (mg)	Maximum responses: Difference in LWG compared to control (range in kg)	Maximum responses: No. of experiments	Maximum responses: Time after treatment (wks)
DES	25	4.9–9.1	3	4–5
Oestradiol	20	4.1	2	3–4
Zeranol	36	0.5–3.4	2	6
Testosterone/oestradiol	200 20	7.6–9.7	4	3–4
Trenbolone acetate/oestradiol	140 20	9.0–15.8	5	4–5
Progesterone/oestradiol	200 20	4.6–7.6	3	3–5

Friesian bull calves were implanted with anabolic agents at 11 weeks of age. The number of animals used in the study was 563. Data from Van der Wal, Berende and Sprietsma [6]. LWG is live-weight gain.

Table 2. Average daily weight gains and feed conversion ratios in cattle following implantation of anabolic agents

Trial	Treatment	Dose (mg)	No. of animals	Period of trial (days)	ADLG (kg/day)	FCR
Steers						
1	Control	—	15	64	0.84	—
	TBA	300	15	64	0.91	—
	Hexoestrol	36	15	64	0.94	—
	TBA/hexoestrol	300/36	15	64	1.17*	—
2	Zeranol	36	8	71	0.76	—
	TBA/zeranol	300/36	8	71	1.00	—
3	Control	—	4	63	0.86	10.2
	TBA	300	3	63	1.02*	9.2
	TBA/oestradiol	140/20	4	63	1.23*	7.4*
Heifers						
4	Control	—	6	56	0.65	13.9
	TBA	300	6	56	1.11*	8.5*

* $P < 0.05$ compared with control value. ADLG is average daily live-weight gain. FCR is feed conversion ratio and TBA is trenbolone acetate. The steers in Trials 1 and 2 were fed 3 kg concentrates per day and maize silage *ad libitum*. The animals in Trials 3 and 4 were fed hay and concentrate according to body weight [13, 14].

used in pigs but oral administration of androgen plus oestrogen is used. Improvement of performance of males can also be achieved by allowing the animals to remain as intact boars.

Poultry

Recently there have been reports that androgens improved growth rate and FCE in young male and female turkeys [10]. Oestrogens have been used for a long time in poultry to produce capons but they do not improve growth rate.

GROWTH PROMOTION IN ADULT ANIMALS

The main use of anabolic agents in the U.K. and U.S.A. is in the fattening of steers and some heifers during the pre-slaughter stage (3–6 months) (for reviews [1, 8]). Anabolic agents are not generally used in bulls, although some initial results show that the performance of bulls can be improved with anabolic agents [12].

A hypothesis to explain the role of sex steroids in the growth rate of cattle suggested that both androgens and oestrogens were necessary to realise the maximum growth rate in cattle [11]. Thus in practice the best responses in growth rate are obtained when androgens are used in females and androgens combined with oestrogens are administered to steers. This is demonstrated by the results shown in Table 2. The growth response in steers following implantation with the synthetic androgen, trenbolone acetate alone was smaller than the response to an oestrogen alone. However, the maximum response in growth rate and improvement in FCE was observed when the androgen was combined with oestrogen. There are similar responses observed in young castrate pigs and sheep.

Use in horses

Anabolic agents are used in horses for the purpose of improving growth in the immature animal and performance in competition rather than increasing meat production. Horses are treated with anabolic agents which are usually androgens, especially testosterone, 19-nor-testosterone and its esters or trenbolone acetate. It is likely that some combination implants of androgen and oestrogen will be used more in the future. Treatment is given to yearlings to improve their muscle development and condition and to older horses to maintain their body condition during training and competition.

MODE OF ACTION OF ANABOLIC AGENTS

The exact mode of action of anabolic agents still remains ambiguous, and it is difficult to identify a simple single mode of action. The common action of all anabolic agents is to increase N-retention. N-balance studies confirmed that anabolic agents with sex-steroid like activity and administered parenterally increased N-retention but they did not alter absorption or metabolism in the alimentary tract [9, 15].

Two modes of action of anabolic hormones can explain the increase in protein accretion in muscle tissue. Anabolic hormones can act directly at the muscle cell by regulating protein synthesis and degradation but they can also act indirectly by modification of a second growth promoting hormone. Both are likely actions of the anabolic hormones.

Mode of action of oestrogens

Considerable evidence supports the view that oestrogens (and progesterone) exert their primary effect at the level of chromatin transcription and gene

expression in cell nuclei of particular target tissues, which include the uterus, liver and chick oviduct. In contrast little is known of the action of oestrogens in skeletal muscle. Studies so far would indicate that oestrogens probably act through the secondary hormones growth hormone (GH) and insulin.

The combination of increased GH and insulin at the muscle cell is thought to increase protein accretion [16]. Injections of GH increase LWG in pigs and probably in young cattle [17].

The implantation of oestradiol-17β in wether sheep caused significant increases in the plasma concentration of GH and insulin [18]. A similar effect was observed with DES in cattle [16]. The primary action of the oestrogen is thought to be on factors controlling the production of GH from the pituitary. The effects on growth of exogenous oestrogen and GH are similar and it is concluded that one of the main influences of oestrogens upon growth, especially in males, is *via* the increased production of GH and insulin.

Mode of action of androgens

The evidence is not conclusive but it is possible that androgens act directly on the muscle cell [19, 20]. Androgens regulate protein synthesis and degradation, resulting in increased protein accretion and decreased rate of protein turnover [21].

This net effect on protein accretion may result from an altered rate of protein degradation. Androgens but not oestrogens [22] are known to displace corticosteroids from their receptor sites. Corticosteroids are potent catabolic agents and may serve a regulatory role in normal growth. It is not inconceivable that androgens may limit this role in animals by substitution at the receptor site for corticosteroids.

A third possible mode of action of androgens is that they act indirectly by regulating the circulating levels of thyroxine. It is known that total circulating levels of thyroxine are dramatically decreased in both cattle [13] and sheep [18] in the presence of androgens and this may be a factor in decreasing protein turnover in muscle cells.

CONCLUSIONS

The differing modes of action of androgens and oestrogens in the regulation of protein metabolism support the hypothesis that to obtain maximum growth the best steroid treatment would maintain physiological concentrations of both androgens and oestrogens in circulating body fluids.

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