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INTRODUCTION

The most common reason for wanting to pharmacologically suppress reproductive activity is to inhibit the expression of sexual or aggressive behaviour in stallions currently used for purposes other than breeding, but for which a subsequent breeding career is envisaged. It is, however, important to note that not all of the components of sexual behaviour are dependent solely on testicular steroid hormones and it is, therefore, not always possible to rid a male horse of unwanted sexual or aggressive behaviour by surgical castration, or by a pharmacological treatment that mimics castration.

Pharmacological stimulation of reproductive activity in stallions is predominantly requested for breeding stallions that show little enthusiasm for their work or apparent dysfunction in one of the components of mating ability. However, because sexual desire and mating performance are complex traits affected in an intricate and highly individual manner by management, psychological, hormonal and physical factors, it is important to establish the background and possible causes of any dysfunction and to determine whether training or correction of an underlying management or health problem are more appropriate than an immediate attempt to treat the presenting symptom. The aim of this presentation is to review the pharmaceutical approaches available for modulating reproductive behaviour in stallions, and to outline the evidence that the treatment in question is preferable to alternative surgical or management approaches, or to doing nothing.

MODULATING REPRODUCTIVE ACTIVITY IN STALLIONS: WHY AND HOW?

Unwanted expression of reproductive or aggressive behaviour

The expression of sexual behaviour by stallions outside the breeding shed is undesirable because it can adversely affect performance or may endanger the handler, rider or others. Fortunately, most young stallions can be taught not to exhibit sexual behaviour in particular circumstances or in response to specific cues. The potential downside to such ‘negative conditioning’ is, as will be discussed later, that when the stallion is subsequently asked to mount a mare or phantom, he may be too scared or confused to perform (McDonnell et al., 1985). If training fails to curb unwanted behaviour in an intact colt or stallion, the classical approach is to remove the source of testicular steroids by surgical castration. Of course, this is undesirable if the animal may later be required as a breeding stallion and, particularly in older animals, it entails appreciable surgical risk. Moreover, surgical castration is not always successful as a means of preventing sexual or aggressive behaviour in horses (Line et al., 1985; Cox, 1986). While the failure of castration to rid older, retired breeding stallions of behavioural patterns that they have learned and reinforced over years of repetition is not surprising, 20-30% of stallions gelded before 2 years of age still go on to develop typical stallion-like sexual behaviour and aggression towards other horses, while around 5% also became aggressive towards people (Line et al., 1985). It follows
that treatments aimed predominantly at inhibiting testicular steroid production may also fail to achieve the desired behavioural suppression in all cases. Nevertheless, such treatments may be useful non-invasive ways of assessing the likely utility of surgical castration for behavioural control in an older stallion. The major pharmacological options described for the suppression of unwanted sexual or aggressive behaviour in stallions are progestagens (Roberts and Beaver, 1987) and GnRH vaccines (Stout and Colenbrander, 2004).

**Suppressing sexual behaviour in stallions using progestagens**

Until recently, the only practical alternative to castration for the suppression of sexual behaviour in stallions was chronic progestagen administration. It is generally assumed that the major effect of progestagen treatment of adult stallions is to suppress hypothalamic and anterior pituitary secretion of GnRH and LH, respectively, and thereby to inhibit testicular androgen production and sexual behaviour (Brady et al., 1997). However, progestagens also appear to exert a direct ‘calming’ effect at a higher (CNS) level (Roberts and Beaver, 1987: Perkins, 2004), which presumably explains why they are also often effective at curbing unwanted sexual or aggressive behaviour in geldings (McDonnell, 2003). Given how frequently progestagens are used in unruly young stallions in practice, there is surprisingly little published about dose rates, efficacy and side effects. Nevertheless, there is evidence that behavioural control can be induced with altrénogest (Regumate™). In this respect, Brady et al. (1997) reported that treating young (2-4 year old) stallions with 0.088 mg/kg altrénogest daily (double the dose recommended for suppression of oestrus in mares) resulted in an inhibition of both libido and aggressive behaviour. On the other hand, Miller et al. (1997) found no evidence of reduced sexual behaviour in older (>5 year old) stallions treated with 0.044 mg/kg altrénogest for 30 days. It, therefore, appears either that older stallions are less responsive, for example because the behavioural response has become ‘hard-wired’, and/or that high circulating concentrations of progestagen are needed to modify behaviour. A number of long acting progestagen implants or injections have also been reported anecdotally to suppress sexual behaviour in stallions and geldings (including delmadinone acetate; Tardak®, the product commonly used for treating hypersexuality in dogs), with the advantage of less frequent administration; however, effective doses, efficacy and side effects have not been studied in controlled trials. Moreover, the ability of many of these products to achieve adequate serum concentrations of bioactive progestagen in horses is questionable, since a number (medroxyprogesterone acetate, hydroxyprogesterone hexanoate, megesterol acetate, norgestomet) are incapable of maintaining pregnancy in mares (McKinnon et al., 2000). The major side effect of treating stallions with progestagens is the suppression of spermatogenesis (Brady et al., 1997). In older stallions, this is unlikely to be a significant and lasting problem; indeed, Miller et al. (1997) found no reduction in sperm production or quality in mature adult stallions treated with altrénogest for 30 days. However, it is not clear whether long-term administration of progestagens to peri-pubertal colts permanently damages spermatogenic capacity. Clearly further studies are necessary to establish which progestagens are most effective for behavioural control, and whether the effects of long-term treatment are fully reversible at the level of spermatogenesis. On a final note of caution, it should be remembered that in many sports, progestagen administration to male horses constitutes a “doping-offence”.

**Suppressing reproductive behaviour in stallions by blocking GnRH activity**

An alternative way of suppressing reproductive activity in stallions is to block the activity of GnRH at its pituitary receptors. In stallions, this has been attempted using GnRH vaccines, antagonists and large doses of agonists (Stout and Colenbrander, 2004).

**GnRH vaccines:** A GnRH vaccine typically comprises GnRH conjugated to a foreign protein that confers antigenicity, and an adjuvant that enhances antibody formation. The anti-
GnRH antibodies raised are thought to bind to endogenous GnRH within the hypothalamic-pituitary portal vessels and prevent it from binding to receptors on the pituitary gonadotropes, thereby removing the stimulus to gonadotrophin secretion (Figure 1). The resulting loss of gonadal stimulation results in a fall in steroid hormone production and consequent reductions in sexual behaviour and spermatogenesis (Stout and Colenbrander, 2004). Schanbacher and Pratt (1985) were the first to report successful GnRH immunization in a stallion, and were suppress testosterone secretion from the abdominal testis of a 3 year-old cryptorchid for 4 months using a series of 5 injections; they concluded that LHRH (i.e., GnRH) vaccination was a useful alternative to surgical castration for suppressing male behaviour in cryptorchids.

In the last 10-15 years, a handful of small studies have examined the effects of various GnRH vaccines on reproductive and behavioural parameters in stallions. While the efficacy of vaccination depends at least in part on the anti-GnRH antibody titre achieved and, therefore, on the exact composition of the vaccine used, the various studies do highlight some general patterns in responsiveness. In young stallions, vaccination reliably induces a rise in circulating anti-GnRH antibody titres, followed by reductions in testosterone concentrations, libido and aggressive behaviour. While FSH secretion is reduced, some autonomous FSH release continues such that spermatogenesis is not completely suppressed.

**Figure 1.** Schematic representations of the endocrinological control of reproduction in (a) a normal stallion and (b) following immunocastration by anti-GnRH vaccination. In vaccinated stallions, GnRH antibodies primarily suppress LH release leading to a sharp fall in testosterone secretion by the Leydig cells; in young stallions, falling testosterone concentrations are reliably accompanied by reductions in libido and aggressive behaviour. While FSH secretion is reduced, some autonomous FSH release continues such that spermatogenesis is not completely suppressed.
that respond to vaccination exhibit the expected decreases in circulating testosterone concentrations, testicle size, sperm production and sperm quality, the effect on behavioural parameters is variable. While Janett et al. (2009) reported a marked reduction in libido in 4 of 5 adult (5-16 year old) stallions, other studies recorded little or no reduction in libido or aggressive behaviour in mature animals (Malmgren et al., 2001; Clément et al., 2005). In a field survey of 22 stallions vaccinated against GnRH for the resolution of behavioural problems, however, owners reported improvement in the majority of stallions presented for inappropriate sexual behaviour (17 of 19), aggression (13 of 15) or distraction (7 of 7) (Burger et al., 2006).

GnRH antagonists: GnRH antagonists suppress the release of gonadotrophins by competitively occupying pituitary GnRH receptors. In stallions, GnRH antagonists have been shown to inhibit secretion of LH and testicular steroids (Hinojosa et al., 2001; Fortier et al., 2002). However, as with GnRH vaccines the behavioural response to suppression appears to be age-dependent; whereas a large single dose of antarelix (100 µg/kg) suppressed libido in young stallions (Hinojosa et al., 2001), daily doses of 10 µg/kg antarelix or cetrorelix for 35-37 days did not affect libido in mature adult stallions despite a dramatic fall in circulating testosterone concentrations (Fortier et al., 2002). Moreover, the use of GnRH antagonists for behavioural control in clinical practice is likely to be limited by the high costs of effective doses.

High doses of GnRH agonists: In a number of species, chronic high-dose administration of a GnRH agonist induces, after an initial gonadotrophin hypersecretion, pituitary desensitization and decreased gonadotrophin release. However, there are species differences in susceptibility to the down-regulatory effects of GnRH agonists, and the available evidence suggests that stallions are fairly resistant to suppression. Moreover, while Boyle et al. (1991) reported that chronic GnRH agonist treatment induced, following a transient stimulation, a suppression of gonadotrophin secretion, testicular steroid production and spermatogenesis in mature stallions, libido was not affected. In addition, Brinsko et al. (1998) were unable to demonstrate any suppressive effects of chronic high dose GnRH administration (25µg every 2 hours for 75 days), while Roser and Hughes (1991) and Sieme et al. (2004) reported the opposite effect, i.e. enhancement of gonadotrophin secretion, sperm quality and libido in animals treated chronically with GnRH outside the physiological breeding season. In short, high doses of GnRH do not appear to be a useful way of suppressing reproductive behaviour in stallions.

STIMULATING REPRODUCTIVE BEHAVIOUR IN STALLIONS: WHY AND HOW?

Stimulating sexual behaviour
Low sexual motivation/libido or poor mating ability are among the more common reproductive complaints in the breeding stallion. In fact, the root cause of the problem often has more to do with previous experience, current health, pain, handling or management than a specific reproductive dysfunction. It is, therefore, generally accepted that pharmacological manipulation to stimulate libido or aspects of mating ability is a last resort to be attempted only when clinical examination, careful observation of management and handling practices, and attempts to train and encourage the stallion have not been successful (McDonnell, 1993). In many cases where “stimulation” of sexual behaviour is the stated requirement, the actual desired effect could more correctly be classified as a relief from psychological obstacles to sexual desire or performance, where these may be the result of previous bad experiences and/or ‘negative conditioning’ to prevent the expression of sexual behaviour during a competitive career (McDonnell et al., 1985). Indeed, for ‘slow-starting’ young stallions, sympathetic handling, patience and an experienced oestrous mare are usually all that is required to overcome initial inhibitions. Similarly, when treatments to reduce anxiety (0.05 mg/kg di-
azepam slow i.v. 5 min prior to breeding) or to temporarily boost libido (50 µg GnRH s.c. 2 h and 1 h prior to breeding) are considered necessary in a novice stallion, they are usually required on only a limited number of occasions (mostly once), because ejaculation is a powerful reinforcing stimulus (McDonnell, 2003). Although the GnRH treatment regime aims to temporarily increase circulating testosterone concentrations, use of exogenous testosterone to boost libido is not generally recommended because too a high a dose risks suppressing spermatogenesis and stimulating aggressive behaviour (circulating testosterone concentrations should be maintained at < 4 ng/ml; McDonnell, 1993).

The reason for poor libido or failure to achieve erection or ejaculation in an experienced breeding stallion is often even more complicated and it is, therefore, essential to fully investigate the background, management factors and/or disease processes that may have contributed to the problem. Common factors include unsympathetic handling, overuse, illness or pain (often musculoskeletal) or, in the case of a stallion used for artificial insemination, an inadequately prepared artificial vagina (e.g. not hot enough, too little pressure). In a small selection of stallions, poor libido may truly be secondary to low circulating androgen concentrations. However, because LH and testosterone secretion show a diurnal pattern, it is recommended that blood samples be collected over the course of at least 8 hours, starting in the morning, if an androgen insufficiency is to be confirmed (Nett, 1993). If proven, low androgen production could be a symptom of the ‘bachelor stallion effect’ described by McDonnell and Murray (1995); that is, a socially mediated suppression in testosterone production and reproductive function in subordinate stallions within a group. Therefore, reducing contact with other stallions and increasing contact with mares might allow recovery of testosterone production and sexual behaviour. While androgen insufficiency has also been hypothesised to arise from insufficiency in hypothalamic GnRH release (hypogonadotrophic-hypogonadism) that, in some cases, can be remedied by chronic pulsatile administration of GnRH (Amann, 1993), this remains an area of contention (e.g. Blue et al., 1991). In addition, care is needed with long-term GnRH administration to avoid suppressing spermatogenesis (Boyle et al. 1991). Nevertheless, chronic GnRH treatment has been reported to improve libido in stallions outside the physiological breeding season (Sieme et al., 2004), by enhancing the seasonally depressed LH and testosterone concentrations (Roser and Hughes, 1991).

CONCLUSIONS

Sexual behaviour problems are common in equine practice and, because the underlying mechanisms are poorly understood, they are challenging to resolve. The suppression of unwanted sexual behaviour in intact stallions can be attempted using GnRH vaccines or progestagens (e.g. altrenogest), but resolution appears to be more likely in young animals (<5 years old). In difficult cases, progestagens may have an advantage because they exert an extra calming effect at the level of the CNS. Enhancement of sexual activity is even more prone to pitfalls. Essentially there are no verified treatments for improving semen quality or fertility, except possibly the chronic administration of GnRH outside the physiological breeding season; even then, care is needed to avoid contradictory suppression of sperm production. Treatments are available to reduce anxiety or to temporarily boost libido in stallions that are slow to show sexual interest, but pharmacological stimulation of sexual behaviour problems with a less obvious origin is generally considered a last resort, and initiated only when the resolution of underlying physical and managemental problems, and gentle retraining, have failed to offer a satisfactory solution.
REFERENCES


