Canine Behaviour – What to do with Problem Dogs Mini Series

Session Three: Pheromones, Medication and Nutraceuticals in Canine Behaviour Modification

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Part 3: Pheromones, medication and nutraceuticals in canine behaviour modification

Study notes

There are a number of products available to augment or support canine behaviour management or modification. These may be recommended by the practice team, the behaviourist or may be chosen spontaneously by the owner. However, they can have variable effects depending on the underlying emotional cause for the behaviour and multitude of factors influencing its development and expression. As such, they should generally only be used once the cause of the behaviour has been diagnosed and alongside appropriate behavioural advice.

The most commonly used products fall into one of three categories: -

- Pheromones
- Prescription medication
- Nutraceuticals/AVM-GSL products

Pheromones

Pheromones are species-specific endogenous chemicals that carry messages to others of the same species. Sites of production and release in the dog are summarised in table 1. Once released they are detected by others via the vomeronasal organ (VNO), which sits in the hard palate behind the incisors. The VNO may be activated by odours, such as the presence of urine, or by scenting behaviour in others. Activation triggers a behavioural response intended to increase absorption. In the dog this may be seen as tonguing: lifting the head and repeatedly pushing the tongue to the roof of the mouth whilst salivating and chattering the teeth (see https://www.youtube.com/watch?v=uccgFbe7bmc). Dogs are also seen to taste the air by moving the head from side to side whilst drawing back the lip commissures. Once within the VNO the pheromones are absorbed and transported by pheromone binding proteins from glands surrounding the VNO to receptors in the VNO body. Impulses are then transmitted to the limbic system where they alter the dog's emotional state and trigger a specific innate behavioural response, which occurs independent of learning.

Synthetic analogues

A synthetic analogue of the canine appeasine produced from the mammary sulcus of the lactating itch and ear of all dogs has been developed and marketed as Adaptiil ™ (Ceva). The claimed effects include reduction or prevention of fear or anxiety related signs and acceleration of desensitisation and counter conditioning due to increased sense of familiarity and security. Evidence supports this. They are suggested to act synergistically with benzodiazepines.

Region of production	Action
Facial glands	Signal social behaviour
Ear	Appeasines from the ceruminous and sebaceous glands signal safety and reassurance
Interdigital glands	Territorial marking and alarm
Inter-mammary sulcus	Appeasines thought to orient neonates and identify areas of safety
Urogenital region	Vulval, preputial and urinary tract secretions signal reproductive receptivity and territorial marking
Circumanal glands	Transmitted via the anal glands by raising the tail or depositing onto faeces. Communicate identity, territorial marking and alarm. Bacterial composition also plays an important role in communication involving anal sac contents

Table 1: Regions of production and activity of principal canine pheromones (Stevenson and Kowalski, 2012; Mills et. al., 2012).

Presentations

The canine appeasine pheromone is available in a number of presentations, each suited to a different use. These are outlined in table 2.

Contraindications

There have been occasional anecdotal reports of adverse behavioural reactions such as avoidance and hyper-excitation. The collar should not be used on sore or broken skin. The pheromone only affects the behaviour of dogs.

Occasionally use of pheromones may increase aggression due to reduced fearful or withdrawal behaviour. Use on one dog in a multi dog household may also disrupt relationships. It may increase confidence in a dog more prone to flight than fight or may make any dogs not wearing the collar excessively curious towards those that are. Care must therefore be taken if there is any conflict between dogs living together. Use in situations where unavoidably stressful handling or treatment will be performed may create mixed signals. For example spray used in a hospital kennel combined with invasive treatment performed in the kennel may confuse the dog about whether it is a safe place or not.

Presentation	Discussion
Pump spray	Primarily suited to transient situations such as car travel, visits to the vets or when introducing a dog to a specific location e.g. a new crate or kennel. It can be applied directly to surfaces or to a bandana placed around the dog's neck. The pheromone is carried in an alcohol base which must be allowed to evaporate before the dog is exposed to it. Each application lasts 2-3 hours.
Diffuser	The pheromone is suspended in a carrier base which is heated and diffused through a unit plugged into a standard electrical socket. It is suited to generalised fear/anxiety that only occurs in the home e.g. house visitors, anxiety based separation related problems and firework phobias. It can also be used to establish a puppy or dog in a new environment e.g. new home, hospital stay, rescue sanctuary. Time needs to be given to allow the pheromone concentration to reach the required saturation after being plugged in. The unit needs to be left on all the time so this is maintained.
Collar	The pheromone is impregnated into a plastic collar. It is recommended for generalised fear or anxiety that occurs outside or both inside and outside the home e.g. fear of strangers, noise sensitivity, traffic, other dogs etc. The collar needs to be in gentle contact with the skin so body heat warms and releases the pheromone. The effect is normally achieved rapidly and lasts for about 4 weeks.

Table 2 Presentations for synthetic dog appeasing pheromones

Prescription medication

Prescription psychotropic medication can change the emotional state of the dog. The principal reasons for opting to use medication in behaviour management or modification are as follows: -

- Short term management for transient problems, such as firework phobias or visiting the vets, or as a first aid measure where the behaviour poses an immediate risk to the animal or others, compromises the animal's quality of life or where time or owner pressure risks the animal being euthanized.
- Re-establishing emotional homeostasis following disruption due to chronic stress or anxiety
- Chemically adjusting the animal's emotional state to facilitate behaviour modification. This may be particularly useful or necessary in long standing behaviours or those that have become entrenched or where behavioural triggers cannot be avoided or sufficiently controlled. Early use of medication may also be indicated in cases of severe compulsions to prevent them becoming habituated whilst behaviour modification is underway.

Collaboration when using medication

Prescription medications can, of course, only be prescribed by the presiding vet. However, unless the vet is also the animal's behaviourist, it is important for there to be collaboration between vet and CAB to ensure the best outcome. Key considerations when prescribing are as follows: -

- The services of a CAB will still be needed to diagnose the cause of the behaviour and advise on behaviour management or modification
- Ideally the CAB will be given the opportunity to assess and diagnose the cause of the behaviour before medication is given. This both ensures the medication does not mask behaviour before this has been observed and that the medication chosen is the right one for the problem.
- The long term aim is usually to wean the animal off the medication once the behaviour is addressed. However in a few rare cases lifelong medication may be indicated.
- Non veterinary CABs are trained to understand how medications affect emotion and behaviour and are able to share this with the presiding vet. They will also have access to resources the vet may find useful when prescribing. However they are not trained to understand how the medications interact with other non-psychotropic medication or concurrent illness. This is entirely the vets domain.

Body systems

The key body systems governing behaviour are the nervous and endocrine systems. Any medication affecting these systems therefore has a potential to impact on behaviour and drugs intended to manipulate behaviour tend to act on these systems.

Drugs acting on the nervous system

Relevant physiology

In brief, whether or not a nerve 'fires', and so triggers other nerves to fire and the animal to perform a specific behaviour, depends in part on the combined influence of multiple neurotransmitters (NTs). NTs are produced and stored in the terminal end of nerve axons. Activation of the nerve will cause NTs to be released and to bind with receptors on the dendrites of the neighbouring nerve. They are then released from the receptor and resorbed back into the axon terminal of the originating nerve Drugs used to modify behaviour via the nervous system typically work by blocking reuptake of NTs, so there is more available to bind with receptors, and increasing the quantity of the receptors for the NT to bind with.

Neurotransmitters relevant to behaviour

The key NTs affecting behaviour are as follows: -

- Adrenaline
  - Controls fight or flight responses
  - Increases cardiac and pulmonary function
  - Increases skeletal muscle function

    - Decreases smooth muscle function

- Noradrenaline
    - Controls fight or flight responses
    - Controls attention and arousal
    - Also influential in the function of the internal reward system

- Dopamine
    - Increases motivation and the sensations of pleasure triggered by rewards
    - Reduces apprehension and so increases exploration and approach
    - Increases attention and confidence
    - Speeds up recovery from fearful episodes
    - Intensifies reward felt from reinforcement, enhancing learning and associated changes in behaviour
    - Improved memory and problem solving

- Serotonin
    - Reduces feelings of anxiety
    - Elevates mood
    - Aids sleep
    - Improves memory
    - Increases sociability and so reduces aggression

- *Gamma* – Aminobutyric acid (GABA)
    - The major inhibitory NT in the CNS
    - Acts on GABA receptors to stop the neuron from firing
    - Acts to inhibit behavioural responses triggered by other NTs

Tri cyclic antidepressants

Tri cyclic antidepressants (TCAs) increase circulating levels of serotonin and noradrenaline by inhibiting reuptake at the synaptic cleft. Over time they also increase the number of serotonin and noradrenaline receptors at the nerve endings, increasing the efficiency of neurotransmitter-receptor binding. The effect of TCAs is to elevate mood due to increased serotonin. However they also act on multiple other NTs leading to side effects in some cases.

The principle TCA used in the UK is Clomipramine hydrochloride (Clomicalm™ (Novartis)), which has a veterinary marketing authority (MA) for use in cases of 'separation anxiety'. However, unwanted behaviour when a dog is left alone can arise due to a number of reasons and so it is important that the emotional cause for the behaviour is determined before the medication is prescribed. Key differentials indicating emotional distress when left include: -

- The behaviour consistently occurs in the owner's absence
- The behaviour does not abate during prolonged absences
- Signs of distress are often seen at the first signs of the owner's imminent departure and soon after they have left.

TCAs have also been shown to significantly reduce compulsive behaviours. Again other possible triggers for apparent compulsive behaviours, such as boredom, physical cause or attention seeking, must be eliminated before use. They are most appropriate where the compulsive behaviour is intense, performance is protracted and the animal cannot be distracted from performing them. Early use is often recommended to avoid development of habit

TCAs may be useful in cases of aggression where this is triggered by fear or anxiety, by preventing heightened fear from blocking treatments such as desensitisation or counter conditioning. However it must be kept in mind that reducing fear or anxiety may, in a few cases, increase the animals choice to use aggression in trigger situations. Particular care is therefore needed to determine cause and evaluate the dog's reaction to reducing fear before prescribing.

Selected serotonin re-uptake inhibitors

Selected serotonin re-uptake inhibitors (SSRIs) inhibit reuptake and increase the number of receptors for serotonin only. Due to their specifity they are up to three times more effective at increasing levels of active serotonin than TCAs. They also have lower side effects.

There are no SSRIs currently marketed for dogs in the UK. Fluoxetine hydrochloride (Reconcile ™ (Eli Lilly) has an EU MA and is used widely in the USA.
Human generic or branded versions (eg Prozac™) are available on veterinary prescription via the cascade

Reconcile is licensed for separation anxiety and also suggested to be effective in cases of fear/anxiety, with or without aggression. Side effects include: -

- Serotonin syndrome caused by excess build up of serotonin
- Transient increase in problem behaviour due to reduction in effective neurotransmission until secondary receptor modification effects occur
- Dependency on inhibition of reuptake to maintain levels. Gradual withdrawal is needed to prevent lows where the drug does not have a long half life

Mono amine oxidase inhibitors

Mono amine oxidase A (MAO-A) is responsible for the reuptake of serotonin, adrenaline and noradrenaline in the dog. MAO-B is responsible for reuptake of histamine and dopamine. Both act on reuptake of phenethylamine which is a releasing agent for noradrenaline and dopamine. Mono amine oxidase inhibitors (MAOIs) inhibit MAO and so increase synaptic levels of these NTs, depending on which MAO they affect.

Selegeline (Selgian ™ (Ceva)) is selective for MAO-B and therefore increases levels of dopamine available at the synaptic cleft. It has a UK MA for behavioural problems of an 'emotional origin' such as overactivity, separation problems, unsocial behaviour, phobias. It Increases reward chemistry, attention, learning, approach and curiosity. It also lessens fearful responses and improves recovery from fear.

It is most effective for behaviours associated with inhibition, avoidance or freezing behaviour, fear, anxiety typified by inhibition or avoidance and sound sensitivity. It is also useful in cognitive impairment due to increased dopamine and other neuroprotective mechanisms.

Behavioural side effects include potential increase in aggression due to disinhibition of aggressive behaviours, increased approach or changes in competitive relationships due to changes in confidence. MOAIs selective for MAO-B are not suited to compulsive behaviours due to intensification of reward.

Benzodiazepines

Benzodiazepines potentiate the binding of GABA, the principal inhibitory neurotransmitter, in the limbic system. The effect is to reduce synaptic firing and associated excitation and anxiety based behaviour. They may also increase social interaction and have mild retrograde amnesic qualities which are effective up to one hour before and for the duration of the treatment. Motor effects are governed by a different receptor set and require a higher dose to emotional effects. As such accurate dosing should enable anxiolysis without ataxia etc.

Disinhibition caused by benzodiazepines may cause increased aggression and occasional paradoxical hyper excitation. There is also an inhibition of learning due to effects on NMDA/glutamate receptors. Examples include alprazolam and diazepam.

Benzodiazepines are useful for short term management of anxiety, such as at the practice, during hospitalisation, car travel or short term a management of firework phobias. They can also be used for transitional management whilst TCA/SSRIs take effect. Their effect on learning means they are not suitable for use during periods of training or desensitisation and counter conditioning, and their potential for tolerance, addiction and rebound effect (return and intensification of symptoms) mean they are not suited to long term use and require gradual withdrawal.

None of the benzodiazepines have an MA in the UK for veterinary use. Alprazalam is short acting but more potent than diazepam. However practitioners are often more familiar with diazepam which improves safety. Diazepam has a rapid onset but is most effective if given 3-4h before event and repeated every 3-6h (short half life). A test dose is recommended at a time when there are no anxiety triggers to determine the optimal dose level and to check for hyperexcitation, aggression disinhibition etc.

Dexmedetomidine

Dexmedetomidine is an alpha 2 agonist which can reduce anxiety without sedation at low doses. Sileo (Zoetis) has a MA for short term use in noise phobias and early research supports efficacy. It does not enjoy the amnesic effects of benzodiazepines, but also has less addictive properties or risk of paradoxical hyperexcitation. Its effect on aggression hasn't yet been researched. However it should be assumed that any drug that changes behaviour has the potential to increase aggression in predisposed dogs.

Drugs acting on the endocrine system

Relevant physiology

The endocrine system regulates hormones that can affect many aspects of behaviour. Those of particular interest in psychopharmacology act on the male reproductive system.

Progestogens
Progestogens primarily play an active role in the reproductive cycle of the bitch. However there are also produced in the male and exogenous progestins (synthetic hormones) can be administered to supress testosterone production. Progestogens are also thought to have calming effect on steroid receptors in the brain.

Delmadinone acetate (Tardak; Pfizer) has an MA for hyper-sexuality (including vagrancy), some forms of aggression and 'nervousness'. Delmadinone has been shown to have a transient beneficial effect on some male typical behaviours. However not all apparent male behaviours are driven by hormones. For example roaming may be due to boredom or habit and mounting may be a social/communicatory behaviour. Removal of behaviour through medication rather than changes in handling and training may result in it being replaced by a different behaviour. For example dogs that are no longer driven to roam may become bored and then destructive or attention seeking. Aggression may be reduced where it is triggered by sexual competition. The intensity and speed may also be reduced in other forms of aggression. However it may inadvertently increase if triggered by fear due to the reduction in confidence associated with testosterone.

Any changes in behaviour may be due to the suppression of testosterone or the inherent calming effect of progestogens and so isn't predicative of the effects of castration.

GnRH agonists
Gonadotropin releasing hormone (GnRH) governs production of reproductive hormones including testosterone. Manipulation can therefore supress testosterone production.

Deslorelin acetate (Suprelorin: Virbac) is a GnRH implant licensed for use to manage canine libido and fertility. However early research suggests it also affects behaviour in a similar way to castration and so is a useful way to assess the likely effect of this (used via the cascade).

The mode of effect means there is a transient increase in testosterone levels before they then reduce. As a result the behaviour change seen over the first 3-4 weeks is typically the opposite of that achieved by castration. If this is likely to be an increase in aggression then appropriate steps need to be taken to manage this. Delmadinone can be administered simultaneously with deslorelin.

Nutraceuticals & AVM-GSL

Alpha-casozepine

Alpha-casozepine is a nutraceutical derived from alpha S1 (άS1) casein in milk. This is recognised to have calming qualities due to its affinity for GABA receptors. The effects of άS1 are greater in neonates as their digestive system favours trypsin over pepsin, which is more efficient at digesting milk. The presentation in pharmacologically prepared alpha-casozepine facilitates adult digestion.

Tests on normal rats and humans showed reductions in stress within 24 hours. Studies of cats and dogs with established anxiety disorders showed gradual improvement over 56 day period. Effects in the first 14 days were low.
Alpha-casozepine is available as Zylkene (Vetoquinol) and in Royal Canine Calm diets.

Valerian

Valerian is a herbal product found to act on melatonin receptors. It therefore increases sleepiness. It also has a possible effect on GABA receptors. Clinical trials show it helps induce onset of sleep and may reduce anxiety or aggression. However production does not enjoy the controls offered by pharmaceutical products and so the chemical composition of plants grown for its production may vary with environment, time of year and regional genetic variations. Different preparation techniques may also affect the final product.

L-Tryptophan

As discussed in session 2, tryptophan is a precursor for serotonin. Increasing the level of tryptophan entering the brain can therefore increase CNS serotonin production and so improve mood. However, as it can also synthesise serotonin outside of the CNS simply increasing intake does not necessarily have the desired effect. Research so far shows little support for the efficacy of oral tryptophan alone to support behaviour modification.

L-Theanine

L-theanine is an amino acid found in green tea and some anxiolytic products aimed at dogs. Research into the behaviour of laboratory beagles given L-theanine did show reduced fearful behaviour around humans. However this has not been repeated or tested outside of the laboratory setting.