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RATIONAL BEHAVIORAL PHARMACOLOGY: CLINICAL APPLICATIONS

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The use of medication should occur and is most effective as part of an integrated treatment program. There is no substitute for the hard work involved in behavior modification; however, some medications may be able to make it easier to implement the modification [1-4]. The newer, more specific, more efficacious drugs have a relatively long lag time between initiation of treatment and apparent changes in the patient’s behavior. This delay is due to the mechanism of action of the tricyclic antidepressants (TCAs) and the selective serotonin re-uptake inhibitors (SSRIs) which employ second messenger systems to alter transcription of receptor proteins.

Serotonin (5-hydroxy-tryptamine [5-HT]): Serotonin receptors are all G-protein-coupled receptors. There are 14 identified classes of serotonin receptors. The 5-HT1 receptors are linked to the inhibition of adenylate cyclase and affect mood and behavior. Presynaptic 5-HT1A-receptors predominate in dorsal and median raphe nuclei; post-synaptic 5-HT1A-receptors predominant in limbic regions (hippocampus and septum) and some cortical layers. Activation of pre-synaptic receptors by agonists results in decreased firing of serotonergic neurons leading to transient suppression of 5-HT synthesis and decreased 5-HT release; activation of post-synaptic receptors decreases firing of post-synaptic cells. These are ‘thermostatic’ effects, not integrated outcomes of receptor activation. The overall effect depends on regulation of second messengers (cAMP, Ca²⁺, cGMP, IP3) and their effects on protein kinases which then alter neuronal metabolism and receptor protein transcription [5]. The subclasses of 5-HT receptors vary in their affects. 5-HT1A receptors affect mood and behavior. 5-HT1D receptors affect cerebral blood vessels and appear to be involved in the development of migraine. These last two classes of receptor subtypes are the primary focus of many behavioral drugs. Urinary excretion of 5-HIAA (5-hydroxy indoleacetic acid) is a measure of 5-HT turnover and has been used to assess neurochemical abnormalities in human psychiatric patients, and has potential in this regard for veterinary behavioral medicine.

Noradrenaline / norepinephrine (NE): The most prominent collection of noradrenergic neurons is found in the locus coeruleus of the grey matter of the pons and in the lateral tegmental nuclei. There is also a cluster in
the medulla. NE has been postulated to affect (1) mood [NE decreases in depression and increases in mania], (2) functional reward systems, and (3) arousal.

Dopamine: The distribution of dopamine in the brain is non-uniform, but is more restrictive than that of NE. Dopaminergic nuclei are found primarily in: (1) the substantia nigra pars compacta which projects to the striatum and is largely concerned with coordinated movement; (2) the ventral tegmental area which projects to the frontal and cingulate cortex, nucleus acumbens, and other limbic structures; and (3) the arcuate nucleus of the hypothalamus which projects to the pituitary. A large proportion of the brain's dopamine is found in the corpus striatum, the part of the extrapyramidal system concerned with coordinated movement.

Dopamine is metabolized by monamine oxidase (MAO) and catechol-O-methyl transferase (COMT) into dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA). HVA is used as a peripheral index of central dopamine turnover in humans, but this use has been little explored in veterinary medicine. All dopaminergic receptors are G-protein-coupled transmembrane receptors. The D1 receptors exhibit their postsynaptic inhibition in the limbic system and are affected in mood disorders and stereotypies. The D2, D3, and D4 receptors are all affected in mood disorders and stereotypies. Excess dopamine, as produced by dopamine releasing agents (amphetamines and dopamine agonists, like apomorphine) is associated with the development of stereotypies.

Gamma amino butyric acid (GABA): GABA, the inhibitory neurotransmitter found in short interneurons, is produced in large amounts only in the brain and serves as a neurotransmitter in ~30% of the synapses in the human CNS. The only long GABA-ergic tracts run to the cerebellum and striatum. GABA is formed from the excitatory amino acid (EEA) glutamate via glutamic acid decarboxylase (GAD), catalyzed by GABA-transaminase (GABA-T) and destroyed by transamination. There are two main groupings of GABA receptors - GABAA and GABAB. GABAA receptors, ligand-gated ion channels, mediate post-synaptic inhibition by increasing Cl- influx. Barbiturates and benzodiazepines are potentiators of GABAA. GABAB receptors are involved in the fine-tuning of inhibitory synaptic transmission: presynaptic GABAB receptors inhibit neurotransmitter release via high voltage activated Ca++ channels; postsynaptic GABAB receptors decrease neuronal excitability by activating inwardly rectifying K+ conductance underlying the late inhibitory post synaptic potential.

GABA also has a variety of tropic effects on developing brain cells. During ontogeny GABAergic axons move through areas where other neurotransmitter phenotypes are being produced, and so may be related to later monoaminergic imbalances.

EAAs (glutamate, aspartate, and, possibly, homocysteate): EEA's have a role as central neurotransmitters and are produced in abnormal levels in aggressive, impulse, and schizophrenic disorders. The main fast excitatory transmitters in the CNS are EEA's. Glutamate, widely and uniformly distributed in the CNS, is involved in carbohydrate and nitrogen metabolism. It is stored in synaptic vesicles and released by Ca2+ dependent exocytosis, so calcium channel blockers may affect conditions associated with increased glutamate. Both barbiturates and progesterone suppress excitatory responses to glutamate. Pre-synaptic barbiturates inhibit calcium uptake and decrease synaptosomal release of neurotransmitters, including GABA and glutamate.
Medications commonly used to treat behavioral conditions in dogs and cats are usually antidepressants and anxiolytics that fall into 3 main classes: the benzodiazepines (BZ), the tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs). Increasingly we see patients treated with serotonin norepinephrine reuptake inhibitors (SNRIs: venlafaxine, duloxetine), serotonin 2A agonist/reuptake inhibitors (SARIs: trazadone, nefazodone), and noradrenergic and specific serotonergic antidepressants (NaSSAs: mirtazapine). Less commonly used medications, or those with more restrictive populations likely to benefit include medications that are monoamine oxidase inhibitors (MAO-Is: selegiline), azapirones (buspirone), centrally acting alpha agonists that are hypotensives (clonidine) and NMDA antagonists (memantine). All of these medications cause their effects through modulation of the neurotransmitters serotonin (5-HT), dopamine (DA), noradrenaline/norepinephrine (NA/NE) and/or gamma amino butyric acid (GABA), and their related metabolites (e.g., the excitatory AA, glutamate, which becomes GABA). Accordingly, any medication that shares a metabolic or synthetic pathway with any of these neurotransmitters or medications can affect the amount of any medications available and their utility.

Because the most severe side effects of TCAs, SSRIs and the more recently popular serotonin 2A antagonist/reuptake inhibitors (SARIs) can involve cardiac affects, clients should and can easily learn to take pulse rates, which may be the first sign of developing serotonin syndrome. Slight increases in pulse rate are not worrisome. Huge, sustained increases in heart rate are problematic. If clients know that their dog’s resting heart rate is 65 bpm and with medication this changes to 150 bpm, they can immediately bring this change to their veterinarian’s attention. Likewise, if the increase is minor (65 to 75 bpm) the client can take notes and not worry. For this reason, baseline ECGs are recommended for any patient who has had a history of any arrhythmia, heart disease, prior drug reactions, is on more than one medication, and who may be undergoing anesthesia or sedation. Use of TCAs is contraindicated in animals with a history of urinary retention, glaucoma and uncontrolled cardiac arrhythmias. The common side effects of TCAs as manifest on ECG include: flattened T waves, prolonged Q-T intervals, and depressed S-T segments [6]. In high doses, TCAs have been implicated in sick euthyroid syndrome. In older or compromised animals complete laboratory evaluations are urged since high doses of TCAs are known to alter liver enzyme levels. Extremely high doses are associated with convulsions, cardiac abnormalities, and hepatotoxicity. Cats are likely to be more sensitive to all TCAs than are dogs because TCAs are metabolized through glucuronidation. Once alerted to potential adverse reactions clients are extremely willing to comply with all monitoring and with the extensive communication needs of behavioral cases. Clients should receive a complete list of all potential adverse responses and should be encouraged to communicate with the clinician at the first sign of any problem. Clients are often very distressed after a behavioral consultation and need a written reminder of situations for which they should be alert.

The cytochrome P-450 system relies on a series of enzymes that are either inhibited or induced by various medications. Enzymes affected by behavioral/psychotropic medications include 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4. Many of these medications also act as substrates for this enzyme system with an especially large number being substrates for the 3A4 enzyme (e.g., alprazolam, amitriptyline, carbamazepine, diazepam, fluoxetine, imipramine, nefazodone, sertaline, trazoldon, triazolam, venlafaxine).

What makes TCAs and SSRIs special and why are they so useful for anxiety disorders? The key to the
success of these drugs is that they utilize the same second messenger systems and transcription pathways that are used to develop cellular memory or to “learn” something. This pathway involves cAMP, cytosolic response element binding protein (CREB), brain derived neurotrophic factor (BDNF), NMDA receptors, protein tyrosine kinases (PTK) - particularly Src - which regulate activity of NMDA receptors and other ion channels and mediates the induction of LTP (long-term potentiation = synaptic plasticity) in the CA1 region of the hippocampus.

There are two phases of TCA and SSRI treatment: short-term effects and long-term effects. Short-term effects result in a synaptic increase of the relevant monoamine associated with re-uptake inhibition. The somatodendritic autoreceptor of the pre-synaptic neuron decreases the firing rate of that cell as a thermostatic response. Regardless, there is increased saturation of the post-synaptic receptors resulting in stimulation of the adrenergic coupled cAMP system. cAMP leads to an increase in PTK as the first step in the long-term effects. PTK translocates into the nucleus of the post-synaptic cell where it increases CREB, which has been postulated to be the post-receptor target for these drugs. Increases in CREB lead to increases in BDNF and tyrosine kinases (e.g., trkB) which then stimulate mRNA transcription of new receptor proteins. The altered conformation of the post-synaptic receptors renders serotonin stimulation and signal transduction more efficient.

Knowledge of the molecular basis for the action of these drugs can aid in choosing treatment protocols. For example, the pre-synaptic somatodendritic autoreceptor is blocked by pindolol (alpha-adrenoreceptor antagonist) so augmentation of TCA and SSRI treatment with pindolol can accelerate treatment onset. Long-term treatment, particularly with the more specific TCAs (e.g., clomipramine) and SSRIs, employs the same pathway used in LTP to alter receptor function and structure through transcriptional and translational alterations in receptor protein. This can be thought of as a form of in vivo “gene therapy” that works to augment neurotransmitter levels and production thereby making the neuron and the interactions between neurons more coordinated and efficient. In some patients short-term treatment appears to be sufficient to produce continued “normal” functioning of the neurotransmitter system. That there are some patients who require life-long treatment suggests that the effect of the drugs is reversible in some patients, further illustrating the underlying heterogeneity of the patient population considered to have the same diagnosis.

When stopping a drug, weaning is preferred to stopping abruptly [7]. A model for how to do this is found below. Weaning minimizes potential central withdrawal signs, including those associated with serotonin discontinuation syndrome [8-9] and allows determination of the lowest dosage that is still effective. Long-term treatment may be the rule with many of these medications and conditions, but maintenance may be at a considerably lower level of drug than was prescribed at the outset. The only way the practitioner will discover if this is so is to withdraw the medication slowly.

Before treating a patient with behavioral medication the veterinarian must ensure that the criteria for diagnosis are met (i.e., the practitioner is addressing a specific diagnosis, not a non-specific correlate or sign) and the relevant pharmacodynamics discussed above are understood and used in the diagnosis.
References


