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Research Paper

Nuclear medicine for the investigation of canine behavioral disorders

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ABSTRACT

The aim of this review was to report the current literature concerning the use of nuclear imaging modalities for the investigation of the neurobiology of canine behavioral disorders. The conventionally used nuclear medicine modalities are positron emission tomography and single photon emission (computed) tomography. At this moment, information is scarce about their application in veterinary behavioral medicine and only present for single photon emission tomography studies in dogs, mainly using ^{99m}Tc-ethyl cysteinate dimer to assess brain perfusion (and indirectly neuronal function) and ^{123}I-5-I-R91150 to evaluate the 5-hydroxytryptamine-2A receptor binding. Current results suggest that functional nuclear imaging provides useful noninvasive in vivo information about the neurobiology and therapeutic evaluation of canine behavioral disorders. Due to striking similarities with neurobiological alterations in human disorders, the dog also represents an interesting natural animal model for human neuropsychiatric diseases.

Introduction

The importance of functional imaging modalities such as single photon emission tomography (SPET) and positron emission tomography (PET) in research on the pathophysiology of behavior and neuropsychiatric disorders has long been accepted in human medicine. These modalities are noninvasive and provide in vivo information on brain perfusion and metabolism, as well as on specific neurotransmitter receptor and/or transporter deficiencies.

Due to the growing general and scientific interest in companion animals and the need to improve diagnosis and therapy, research in behavioral disorders in dogs has become more and more important. In addition, the investigation of the neurobiological base of canine behavioral disorders and the extent to which canine behavioral disorders overlap with human disorders may be interesting from the perspective of the dogs as a natural animal model (Overall, 2000).

The goal of this article was to review the literature dealing with SPET and PET imaging in the investigation of the pathophysiology of canine behavioral disorders, such as impulsive aggression, anxiety, and compulsive disorders, and to discuss overlap between canine and human disorders. Similar patterns of behavioral disturbances are seen in related major human mental illnesses. In this article, we will also review the use of nuclear medicine imaging as a modality to monitor the effect of psychopharmaceutic drugs on neurotransmitter systems.

Functional imaging of the normal canine brain

Brain perfusion using SPET

The regional brain perfusion is the blood supply to a specific brain region in a given period, which depends on the cerebral perfusion pressure and the cerebral vascular resistance. The regional cerebral blood flow reflects neuronal function and is therefore an indirect tool to measure regional brain function (Roy and Sherington, 1890).

Both ^{99m}Tc-hexamethylpropylene amine oxime and ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) can be used to evaluate regional brain

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perfusion using conventional collimated gamma cameras in dogs (Leblanc and Peremans, 2014). Both tracers are trapped inside the neuron within minutes after injection with a brain distribution that depends on regional brain perfusion and function to create so-called "frozen images." These compounds can be injected during seizures, while the patient is performing tasks or during drug challenges. The images can be obtained after a time lag and will reflect neuronal activity at the moment of injection.

Care has to be taken when selecting a tracer because significant regional differences in uptake have been identified in the canine brain in subcortical regions and to a lesser extent in the cerebellum (Adriaens et al., 2013). These differences in regional uptake may be explained by the difference in intracellular trapping mechanism: ^{99m}Tc-ECD depends on esterase activity and ^{99m}Tc-hexamethylpropylene amine oxime on glutathione availability and redox equilibrium (Jacquier-Sarlin et al., 1996a; Jacquier-Sarlin et al., 1996b). Therefore, although both tracers can be used for evaluation of the cerebral blood flow in dogs, their differences in regional distribution limit direct comparison between them (Adriaens et al., 2013).

Injection of the radiopharmaceuticals must be performed in quiet surroundings with dimmed lights to prevent activation of certain brain regions by sensory stimuli. Whenever possible, radiotracers should also be injected before sedation and anesthesia because they influence the regional cerebral blood flow. The effect of medetomidine on tracer trapping has been previously described (Waelbers et al., 2011) and has to be taken into account when comparing imaging results with the tracer injected before sedation and those when the tracer is injected under sedation. In dogs, the optimal image acquisition time interval is 15 to 40 minutes after radiotracer injection, a time at which both trapping mechanisms have functioned, and washout is still low, resulting in stable uptake of the tracer with respect to the quantification procedure. The uptake and washout rate in dogs is faster than what is reported in humans (Ichise et al., 1997; Waelbers et al., 2012).

The regional cortical and subcortical distribution is evaluated by means of a perfusion-binding index. The perfusion-binding index reflects the regional neuronal activity and is estimated as the regional activity normalized to the total brain activity, practically calculated as (counts/pixel in the regional region of interest)/(counts/pixel in all region of interests).

The normal regional distribution pattern of ^{99m}Tc-ECD was first described using conventional fan-beam single photon emission (computed) tomography in 2001 by Peremans et al., demonstrating highest perfusion in the subcortical region compared to a rather homogeneous cerebral uptake, and a rostrocaudal gradient with lowest uptake in the frontal cortices (Figure 1; Peremans et al., 2001). A similar rostrocaudal gradient is reported in humans with the highest uptake in the caudal brain regions (occipital lobes), and the lowest uptake in the frontocortical regions (Koyama et al., 1997).

The regional distribution of this radiotracer was later evaluated with micro-SPECT using a conventional triple-head gamma camera equipped with 3 multipinhole collimators, to increase image resolution and define some brain regions in more detail as part of a study on epilepsy. This study confirmed the presence of a negative rostrocaudal gradient (Martlé et al., 2014).

Canine global cerebral perfusion decreases with aging, with a significant regional decrease within the frontal, temporal, and subcortical regions (Peremans et al., 2002a). These findings are similar to human studies that report a global reduced brain perfusion with significant regional decreased perfusion in the prefrontal and temporal cortex in the elderly (Markus et al. 1993; Van Laere et al. 2001). No significant alterations were found in the caudal brain areas in dogs, similar to humans, suggesting that these brain regions may be less vulnerable to aging effects (Peremans et al., 2002a; Van Laere et al., 2001).

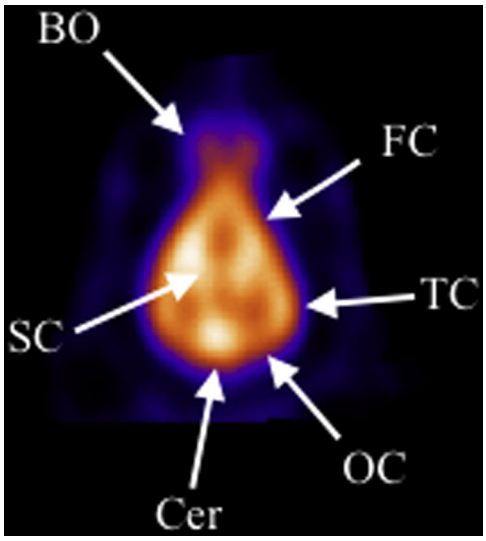

Figure 1. ^{99m}Tc-ECD scan of the brain of a normal dog. Dorsal image of the brain of a healthy dog after administration of the perfusion radiotracer ^{99m}Tc-ECD (orange representing high radioactivity concentration and blue low radioactivity concentration on this color scale). ^{99m}Tc-ECD, ^{99m}Tc-ethyl cysteinate dimer; BO, bulbus olfactorius; Cer, cerebellum; FC, frontal cortex; OC, occipital cortex; SC, subcortical area; TC, temporal cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

No sex influence on regional brain perfusion was noted in dogs (Peremans et al. 2002a), whereas a difference has been reported in humans (Van Laere et al., 2001).

Neuroreceptor imaging using SPET

The principle of neuroreceptor imaging is to evaluate receptor behavior in vivo with injection of ligands labeled with radioactive isotopes. Neuroreceptor imaging is used in dogs to evaluate pathophysiology of behavioral disorders and the effectiveness of pharmacotherapy. SPET imaging was reported in healthy dogs to evaluate the 5-hydroxytryptamine-2A (5-HT$_{2A}$) receptor using ^{123}I-5-I-R91150 (Peremans et al., 2002a; Peremans et al., 2002b; Peremans et al., 2003b), the serotonin transporter (SERT), and dopamine transporter (DAT) using ^{123}I-2β−carboxymethoxy-3β−(4−iodophenyl)tropane (^{123}I-β-CIT) and ^{123}I-N-(3-fluoropropyl)-2β−carboxymethoxy-3β−(4−iodophenyl)nortropane (^{123}I-FP-CIT) (Peremans et al., 2006; Vermeire et al., 2011a).

The regional binding index (BI) is estimated as (counts/pixel in the region of interest)/(counts/pixel in the reference region). The reference region used for the serotonergic and dopaminergic systems is the cerebellum because of its very low density in 5-HT$_{2A}$, SERT, and DAT (Cortes et al., 1988; D'Amato et al., 1987; Hall et al., 1999). The calculated BI is a measure of the number of receptors/transporters in the different brain regions. The DAT density can also be assessed by measuring striatal uptake ratios using a resolution-independent method: right striatal uptake ratio = (right striatum^{counts}−(BG^{counts} × right striatum^{cm3}BG^{cm3}))/(BG^{counts}/BG^{cm3}) with BG^{counts} = brain activity^{counts}−left and right striatal activity^{counts} (Goethals et al., 2007).

As mentioned previously, neither regional cerebral perfusion nor regional neuroreceptor distribution is uniform throughout the canine brain. This distributional pattern raises the possibility that brain perfusion and receptor distribution could interact and affect SPET measurements of receptor density. Fortunately, no correlation was demonstrated between alterations of regional brain perfusion and BI of the neuroreceptor radioligands, providing evidence that