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RESEARCH PAPER

Modulation of nociceptive withdrawal reflexes evoked by single and repeated nociceptive stimuli in conscious dogs by low-dose acepromazine

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Abstract

Objectives To investigate the modulation of the nociceptive withdrawal reflex (NWR) and temporal summation (TS) by low-dose acepromazine (ACP) in conscious dogs. To assess the short- and long-term stability of the reflex thresholds.

Study design Randomized, blinded, placebo-controlled cross-over experimental study.

Animals Eight adult male Beagles.

Methods The NWR was elicited using single transcutaneous electrical stimulation of the ulnar nerve. Repeated stimuli (10 pulses, 5 Hz) were applied to evoke TS. The responses of the deltoideus muscle were recorded and quantified by surface electromyography and the behavioural reactions were scored. Each dog received 0.01 mg kg^{-1} ACP or an equal volume saline intravenously (IV) at 1 week intervals. Measurements were performed before (baseline) and 20, 60 and 100 minutes after drug administration. Sedation was scored before drug administration and then at 10 minutes intervals. Data were analyzed with Friedman repeated measures analysis of variance on ranks and Wilcoxon signed rank tests.

Results Acepromazine resulted in a mild tranquilization becoming obvious at 20 minutes and peaking 30 minutes after injection. Single (I_t) and repeated stimuli (TS_t) threshold intensities, NWR and TS characteristics and behavioural responses were not affected by the ACP at any time point. Both I_t and TS_t were stable over time.

Conclusions and clinical relevance In dogs, 0.01 mg kg^{-1} ACP IV had no modulatory action on the NWR evoked by single or repeated stimuli, suggesting no antinociceptive activity on phasic nociceptive stimuli. The evidence of the stability of the NWR thresholds supports the use of the model as an objective tool to investigate nociception in conscious dogs. A low dose of ACP administered as the sole drug, can be used to facilitate the recordings in anxious subjects without altering the validity of this model.

Keywords acepromazine, nociception, NWR, stability, temporal summation.

Introduction

Understanding and treating pain in animals is a very challenging task in veterinary medicine. One of the major difficulties is assessment of pain in conscious animals (Paul-Murphy et al. 2005). In an

attempt to solve this problem, the nociceptive withdrawal reflex (NWR) has been described as a non-invasive experimental model to investigate nociception in conscious horses (Spadavecchia et al. 2002, 2003, 2004, 2005; Knobloch et al. 2006) and dogs (Bergadano et al. 2006, 2007). The NWR is a polysynaptic spinal nociceptive reflex, and represents the mechanism for withdrawing an extremity from injury (Sherrington 1910). It is possible to elicit the reflex by transcutaneous electrical stimulation of a sensory peripheral nerve and to record the withdrawal reaction by the electromyographic (EMG) response from the activated muscles. The NWR is reproducible, stimulus-dependent and correlates with the intensity of subjective pain perception in humans (Willer 1977) making it a useful tool for pain research in humans (Arendt-Nielsen et al. 2000). By applying appropriate repetitive stimulation patterns, temporal summation (TS) of the reflex can be evoked and quantified (Dimitrijevic & Nathan 1970; Price 1972; You et al. 2003). Temporal summation in humans is an experimental model of the early process of wind-up and can be used to study and quantify aspects of central integration (Andersen et al. 2005). Wind-up is one method for inducing a long lasting state of neuronal hyperexcitability which may lead to the development of chronic pain states (Woolf 1983, 1984). In humans, there is ongoing research using the NWR and temporal summation as objective tools to detect and quantify central hyperexcitability in individual patients (Desmeules et al. 2003; Banic et al. 2004; Curatolo et al. 2004). In the same way, the NWR and TS could be used as tools to detect and quantify the degree of sensory dysfunction in dogs affected from chronic malignant or nonmalignant conditions (Hielm-Björkman et al. 2003; Beckman 2006). Furthermore, this neurophysiological model could be employed to assess objectively the efficacy of antinociceptive treatments in individual dogs which would finally improve in the therapeutic strategies in animals affected by chronic pain. While implementing this model in clinical practice, it has to be considered that dogs will probably not lie quietly to allow instrumentation and recording, especially if affected by chronic musculoskeletal pain. Therefore, to augment their compliance to the measurement technique and well-being and to reduce stress, the pre-emptive administration of a neuroleptic drug would be indicated. The ideal drug should be anxyolitic, and devoid of any antinociceptive action which could exert a modulatory effect on the test and alter its validity. Acepromazine (ACP), a phenothiazine tranquillizer commonly used in dogs as a neuroleptic, is considered to possess all of these characteristics (Pugh 1964; Barnhart et al. 2000; Gross 2001; Vaisanen et al. 2002). As a primary aim, a low-dose of ACP (Plumb 2002) was hypothesized not to affect the NWR and TS characteristics in conscious dogs. Moreover, if within-subject variations in individual NWR thresholds are to be attributed to modifications in central excitability or to antinociceptive drugs, it is important to show that the thresholds remain stable over time (French et al. 2005). Therefore as a secondary aim, we analyzed the short-term (within session) and the long-term (1 week) variability of I_t and TS_t. To date, there are no published data on NWR measurement reliability in dogs.

Methods

The experiments were approved by the committee for animal experimentation of the canton Basel city, Switzerland (approval number 2090).

Animals and instrumentation

Eight adult male purpose-bred Beagles with a mean (range) body mass of 9 (7.6–13) kg and 2.4 (1.5–5) years old were studied. They were judged to be healthy on the basis of physical examination and clinicopathologic analyses. The dogs were housed together in runs and food was withheld on the morning of the experimental session.

The stimulation and recording sites were clipped, shaved and degreased. The dogs were then positioned in right lateral recumbency on a comfortable dog bed, with the limbs extended laterally in a natural position but not supported, and without weight bearing or movement restriction of the nondependent limb. Self adhesive stimulation electrodes (Neuroline 700 05-j; Medicotest A/S, Olstykke, Denmark) were placed over the left ulnar nerve (ramus dorsalis), and the ground electrode (Synapse 32 mm; Ambu A/S, Ballerup, Denmark) was placed over the plantar side of the right foot. The recording electrodes (Neuroline 700 05-j; Medicotest A/S) were positioned on the deltoid muscle. Flexible leads were connected to the electrodes. The resistance of each electrode pair was checked and confirmed to be <5 kΩ before beginning and at the end of each experimental session

