Published in final edited form as:
Neurosci Lett. 2013 October 25; 555: . doi:10.1016/j.neulet.2013.09.013.

Blockade of B_2 Receptors attenuates the responses of group III afferents to static contraction

Anna K. Leal[a,*], **Audrey J. Stone**[a], **Katsuya Yamauchi**[a], **Jennifer L. McCord**[a], and **Marc P. Kaufman**[a]

[a]Heart and Vascular Institute, Penn State College of Medicine, Hershey PA 17033

Abstract

Recent evidence has been presented demonstrating that group III mechanoreceptors comprise an important part of the sensory arm of the exercise pressor reflex, which in turn functions to increase arterial blood flow to contracting skeletal muscles. Although Group III afferents are stimulated by mechanical distortion of their receptive fields, they are also stimulated by bradykinin, which is produced by skeletal muscle when it contracts. Moreover, blockade of B (bradykinin)$_2$ receptors has been shown to decrease the magnitude of the exercise pressor reflex. Nevertheless, the effect of blockade of B_2 receptors on responses of group III afferents to contraction is not known. We therefore determined the effect of B_2 receptor blockade with HOE 140 (40 μg/kg) on the responses to both static and intermittent contraction of group III afferents with endings in the triceps surae muscle of decerebrated unanesthetized cats. We found that HOE 140 significantly attenuated (P= 0.04) the responses of 14 group III afferents to static contraction, but did not significantly attenuate (P= 0.16) the responses of 16 group III afferents to intermittent contraction. The attenuation induced by HOE 140 was present throughout the static contraction period, and led us to speculate that blockade of B_2 receptors on the endings of group III afferents decreased their sensitivity to mechanical events occurring in the working muscles.

Keywords

HOE 140; exercise pressor reflex; mechanoreception; bradykinin; locomotion

1. Introduction

The exercise pressor reflex, which is evoked by contracting skeletal muscles, increases arterial pressure, heart rate, sympathetic nerve discharge in animals and humans [1] [2] [3] [4] [5] [6] [7] [8] [9]. The afferent arm of the reflex arc is comprised of thinly myelinated group III afferents, which respond primarily to mechanical stimuli, and unmyelinated group IV afferents, which respond primarily to metabolic stimuli [2] [10] [11] [12]. The afferents evoking the reflex were believed to signal that the oxygen/blood supply to the exercising muscles was not adequate to meet its metabolic demand [5] [13]. The exercise pressor reflex, in turn, was believed to increase perfusion of the contracting muscle by increasing cardiac output and vascular resistance to non-exercising muscles and viscera [14] [15].

*Corresponding author at: Anna K. Leal, Penn State College of Medicine, 500 University Drive, Hershey, PA 17033, Tel: (717) 531-0003 x 283998, aleal@hmc.psu.edu.

These findings resulted in investigations focusing on the responses of group IV afferents to administration of putative metabolites believed to be generated by a mismatch between oxygen/blood supply and demand during exercise [16] [17] [18] [19] [20].

Recent evidence has shown that group III mechanoreceptors also play a significant role in the generation of the exercise pressor reflex [4]. For example, gadolinium-induced blockade of mechanogated channels on group III afferents attenuated the reflex pressor and sympathetic nerve responses to static contraction [21] [22] [23]. Although gadolinium attenuated the responses of group III mechanoreceptors to contraction and stretch, it had no effect on their responses to bradykinin [23]. In addition, gadolinium had no effect on the responses of group IV metaboreceptors to contraction, a finding which further supported the selective effect of this agent on mechanogated channels [23]. Nevertheless, the mechanical sensitivity of group III afferents can be influenced by the chemical milieu surrounding their endings. For example, the responses of group III mechanoreceptors to static contraction were attenuated by indomethacin, an agent which decreased the production of prostaglandins and thromboxane by the exercising muscles [24] [25] [26]. Likewise, the responses of group III afferents to mechanical distortion of their receptive fields can be increased by prior administration of bradykinin [27], an autocoid whose concentration in skeletal muscle is increased by its contraction [28].

Several lines of evidence indicate that bradykinin plays a role in the generation of the exercise pressor reflex. For example, blockade of the enzyme that synthesized bradykinin in skeletal muscle attenuated the exercise pressor reflex [29]. Moreover, blockade of the enzyme that degraded bradykinin exaggerated the reflex [29]. In addition, blockade of bradykinin $_2$ receptors (B_2) in contracting skeletal muscles attenuated the exercise pressor reflex [30]. Last, injection of bradykinin into the arterial circulation of hindlimb muscles of cats stimulated group III afferents, which were also mechanosensitive, [10] [17] as well as evoked reflex pressor responses [31]. Despite these findings, the role played by bradykinin in stimulating group III afferents during contraction is not known. We were prompted, therefore, to determine the effect of blockade of B_2 receptors on the responses of group III afferents to static and intermittent contraction of the triceps surae muscles.

2. Methods

All procedures were approved by the Institutional Care and Use Committee of the Pennsylvania State College of Medicine.

Surgical preparation—Anesthesia was induced in 39 female cats (2.9 ± 0.1 kg) with 5% isofluorane in oxygen. The trachea was cannulated, and the lungs were ventilated mechanically with 3% isofluorane in oxygen. Catheters were placed in the right jugular vein and common carotid artery, with the latter being used to measure arterial pressure.

The cat was placed in a Kopf stereotaxic and spinal unit and then given dexamethasone (4 mg IV). A midcollicular decerebration was performed, and all neural tissue rostral to the section was removed. The cranial vault was filled with agar (37°C). A laminectomy was performed, the left triceps surae muscles were isolated, and the calcaneal bone was cut. The free end of the calcaneal tendon was attached to a force transducer to measure tension development. All visible branches of the left sciatic nerve innervating the thigh and hip as well as the left femoral nerve were cut. Anesthesia was terminated after the surgery was completed, but in some instances where the cat displayed excessive activity when the ventral roots were stimulated, we ventilated the lungs with 0.5% isofluorane in oxygen.

2.1 Recording of impulse activity from group III and IV afferents

The impulse activity from group III afferents with endings in the left triceps surae muscles was recorded from filaments dissected from the L_7 or S_1 dorsal roots. The afferent signals were passed through a high-impedance probe, amplified and filtered (100 3,000 Hz). Action potentials were displayed on a computer monitor (Spike 2).

The conduction velocity of an afferent was calculated by dividing the conduction distance between the recording electrode and the stimulating electrode on the tibial nerve by the conduction time. Afferents conducting impulses between 2.5 and 30 m/s were classified as group III afferents [10]. The receptive fields of the afferents were located in the triceps surae muscles by either gently stroking the muscle or squeezing it in a non-noxious manner. Afferents conducting impulses greater than 30 m/s were tested for their responses to muscle twitch which was evoked by single pulse stimulation of the ventral roots; the ones that were stimulated by twitch were classified as group Ib afferents (i.e., Golgi tendon organs) and the ones that were inhibited were classified as group Ia or II afferents (i.e., spindles) and were discarded.

The triceps surae muscles were contracted by electrical stimulation (15 20 Hz; 0.1 ms; 2–3 time motor threshold) of the cut peripheral ends of the L_7 and S_1 ventral roots. Two types of contraction were used. The first was static contraction, which was evoked by a maintained stimulation of the ventral roots for 45 seconds. The second was intermittent contraction, which was evoked by stimulation of the ventral roots for 0.5 seconds followed by no stimulation for 0.5 seconds until 45 seconds had elapsed.

2.2. Experimental protocol

We recorded group III and Ib afferent activity during both static and intermittent contraction. The order of the two types of contraction was varied randomly and the interval between the two contractions was at least 10 minutes. If an afferent appeared to be stimulated by either contraction, we injected the B_2 receptor antagonist, HOE 140 (40 μg/ kg) into the right carotid artery. HOE 140 is more than 1000 fold more selective for the B_2 receptor than for the B_1 receptor [32]. The dose of HOE 140 used was greater than that used previously (i.e., 30 μg/ kg) [30]. Twenty minutes after injecting HOE 140, we initiated the two contraction protocols. In previous experiments in cats, we demonstrated that the responses of group III afferents to contraction of the triceps surae muscles were repeatable if no antagonist was given [33].

2.3. Data analysis

Baseline activity of each afferent was counted for the 30 second period immediately preceding either static or intermittent contraction. Likewise, activity of the afferent was counted for the 45 second period of contraction. Our criterion for stimulation of a group III afferent by either type of contraction was an increase in activity of >12 impulses in 45 s. The tension time index (TTI) [34] was calculated by integrating the area between the tension trace and its baseline level. All values are expressed as means ± SE. Two-way repeated-measures ANOVA followed by Scheffe post hoc tests were used to determine statistical significance, the criterion for which was $P < 0.05$.

3. Results

We recorded the impulse activity of 22 group III afferents with endings in the triceps surae muscles (conduction velocity: 13.8 ± 1.5 m/s; range: 2.7–26.2 m/s). The responses to static contraction were tested in each of the 22 group III afferents; likewise, the responses to intermittent contraction were tested in 19 of the 22 afferents.

3.1 Effects of HOE 140 on the responses of group III and group Ib afferents to static contraction

Static contraction of the triceps surae muscles stimulated 14 of the 22 group III afferents tested. On average, B_2 receptor blockade significantly decreased the responses of the 14 group III afferents responding to static contraction (P= 0.04); nevertheless, contraction still increased the discharge of the 14 afferents over their baseline levels after injection of HOE 140 (P= 0.02; Figures 1, 2 and 3). On an individual basis, B_2 receptor blockade attenuated the responses to static contraction of 12 of the 14 afferents tested. The tension time indices before and after HOE 140 averaged 165 ± 20 kg seconds before and 164 ± 17 kg seconds afterwards (P= 0.93; n=14). The conduction velocity of the 14 group III afferents responding to contraction averaged 15.1 ± 2.0 m/s, whereas the conduction velocity of the eight group III afferents not responding to contraction averaged 11.5 ± 2.0 m/s (P= 0.25). The attenuating effect of HOE 140 was present throughout the entire contraction period (Figure 3).

HOE 140 had no effect on the responses of six group Ib afferents to static contraction (conduction velocity: 46 ± 3 m/s). The TTIs before and after HOE 140 averaged 237 ± 53 kg s and 218 ± 57 kg s, respectively (P= 0.42).

3.2 Effects of HOE 140 on the responses of group III and group Ib afferents to intermittent contraction

Intermittent contraction of the triceps surae muscles stimulated 16 of the 19 group III afferents tested. On average, B_2 receptor blockade had no significant effect on the responses of the 16 group III afferents responding to intermittent contraction (P=0.16). On an individual basis, B_2 receptor blockade appeared to decrease the responses of 12 of the 16 group III afferents, but the effect was small and overall was not statistically significant (Figures 1 and 3). The conduction velocity of the 16 group III afferents responding to intermittent contraction averaged 12.1 ± 1.6 m/s, whereas the conduction velocity of the three group III afferents not responding to contraction averaged 13.2 ± 3.1 m/s (P= 0.79). The tension time indices before and after HOE 140 averaged 89 ± 18 kg seconds before and 99 ± 19 kg seconds afterwards (P= 0.12; n=16).

HOE 140 (40μg/kg) had no effect on the responses of six group Ib afferents to intermittent contraction (conduction velocity: 46 ± 3 m/s). The TTIs before and after HOE 140 averaged 75 ± 9 kg s and 97 ± 26 kg s, respectively (P= 0.52).

4. Discussion

Bradykinin stimulates two types of receptors on primary afferents. The first, termed B_1, is inducible; under normal conditions its level is low, although during inflammation or injury its level increases. The second receptor, termed B_2, is constitutive and is therefore found on primary afferents in normal conditions [35] [36]. Only the B_2 receptor has been shown to play a role in the generation of autonomic reflexes arising from skeletal muscle [30] [37]. Group III afferents comprise part of the afferent arm of the exercise pressor reflex [2] [12]. The role played by bradykinin in stimulating group III afferents during contraction is unknown. However, injection of bradykinin into the arterial supply of muscle stimulated the same group III afferents that are stimulated by contraction [10] [38] [27] [17]. These findings prompted us to investigate the effect of blockade of the B_2 receptor on the responses of group III afferents to contraction. We found that blockade of B_2 receptors with HOE 140 significantly decreased the responses of group III afferents to static contraction, but had no significant effect on their responses to intermittent contraction.

The doses of bradykinin used previously to stimulate group III afferents seemed large, raising the possibility that they created concentrations in the muscle that exceeded those created during contraction [10] [38] [17]. Our findings using a B_2 receptor antagonist demonstrated that bradykinin significantly contributed towards stimulating these thinly myelinated afferents during static contraction. Our findings, nevertheless, suggest that this contribution is modest because much of the response to static contraction by these afferents remained after administration of HOE 140. One interpretation of this finding is that blockade of B_2 receptors prevented bradykinin from sensitizing group III afferents to static contraction. Bradykinin-induced sensitization of group III afferents has been shown for other stimuli such as stretch and mechanical distortion of receptive fields [27]

We can only speculate as to why blockade of B_2 receptors in our experiments reduced the responses of group III afferents to static contraction, but had no statistical effect on their responses to intermittent contraction. One explanation is that static contraction produced more bradykinin in the working muscles than did intermittent contraction. Support for our speculation comes from the fact that static contraction resulted in a higher TTI than did intermittent contraction. As a consequence, metabolism was likely to be higher and arterial blood flow was likely to be lower in muscles contracting statically than in muscles contracting intermittently. Both factors probably contributed to the generation of bradykinin by contracting skeletal muscle [28]. A second explanation is that the higher blood flow to the triceps surae muscles during intermittent contraction was higher than during static contraction and resulted in more washout of bradykinin.

Group Ib afferents are known to be stimulated by contraction, but their stimulation has no reflex autonomic effects. Group Ib afferents, therefore, do not play a role in evoking the exercise pressor reflex [2] [12]. In addition, group Ib afferents are not stimulated by doses of bradykinin that vigorously stimulate group III afferents [38]. These findings lead to the prediction that HOE 140 would have no effect on the responses of group Ib afferents to either static or intermittent contraction. We confirmed this prediction in our experiments.

The contraction-induced release of bradykinin by skeletal muscle can stimulate group III afferents by two mechanisms, namely by a direct action on B_2 receptors and an indirect action by producing cyclooxygenase metabolites of arachidonic acid. Substantial evidence exists that cyclooxygenase products, such as prostaglandin E_2 and thromboxane A_2, either directly stimulate group III muscle afferents or sensitize them to static contraction [16] [33] [39]. Nevertheless, bradykinin-induced prostaglandin and thromboxane production requires activation of B_2 receptors [40], which were blocked by HOE 140 in our experiments. Consequently, any bradykinin-induced prostaglandin and thromboxane production by the contracting muscles was probably prevented by HOE 140. Nevertheless, prostaglandin and thromboxane production by mechanisms other than bradykinin release by muscle still were available to stimulate group III afferents during contraction.

Our experiments have two important limitations. The first is that we did not challenge the efficacy of blockade by HOE 140. The dose of HOE 140 used, however, was one third larger than that used previously to abolish the pressor response to bradykinin injection into the arterial supply of hind limb muscle in cats [30]. The second limitation is that we did not examine the effect of B_2 receptor blockade on the responses of group III afferents to ischemic contraction. We have previously shown, however, that ischemia does not increase the discharge of group III afferents to static contraction [11]. In fact, ischemia sometimes decreased their responses to static contraction because a lack of arterial blood flow decreased the ability of the muscles to develop tension, which in turn decreased the amount of mechanical distortion to the afferents' receptive fields. We speculate that the decrease in

mechanical stimulus to the group III afferents countered the increase in bradykinin production induced by ischemia [28].

In summary, we have shown that blockade of B_2 receptors on the presumptive endings of group III afferents attenuated their responses to static contraction, but had minimal effect on their responses to intermittent contraction. Our findings confirm and extend previous evidence that bradykinin plays a role in evoking the exercise pressor reflex [28] [30]. This attenuating effect appears to present throughout the period of static contraction, and is consistent with the speculation that bradykinin production functions to sensitize group III afferents to mechanical stimulation.

Acknowledgments

This work was supported by NIH grant HL 30710. We thank Ms. Joyce Kim for her technical assistance.

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Highlights

- The exercise pressor reflex is driven, in part, by group III mechanoreceptors.
- Bradykinin$_2$ receptor blockade attenuated group III responses to static contraction.
- B_2 blockade had no effect on group III responses to intermittent contraction.
- Our data suggests that bradykinin helps evoke the exercise pressor reflex.

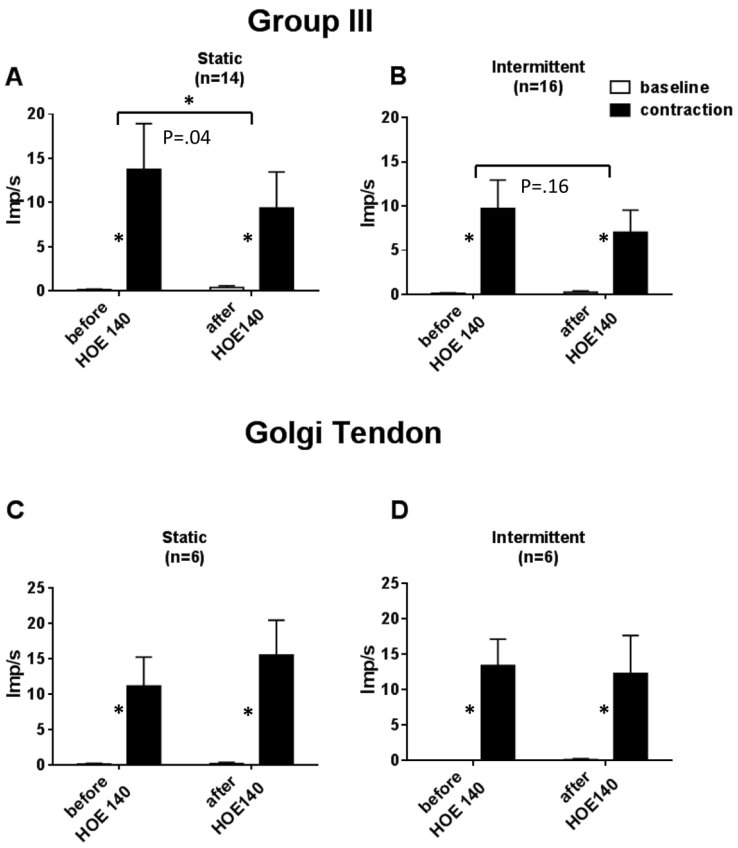

Figure 1.

Summary data showing the responses of group III and Ib afferents to static and intermittent contraction before and after HOE 140 (40μg/kg). Open bars represent baseline activity. Filled bars represent the discharge of the afferents during the contraction period. Asterisks represent a significant ($P < 0.05$) contraction-induced increase in activity over baseline levels. Horizontal brackets connect differences between responses to contraction and baseline before and after HOE 140. Note that HOE 140 significantly reduced ($P < 0.04$) the group III responses to static contraction (bracket with asterisk), but had no statistical effect on the group III responses to intermittent contraction (bracket with no asterisk).

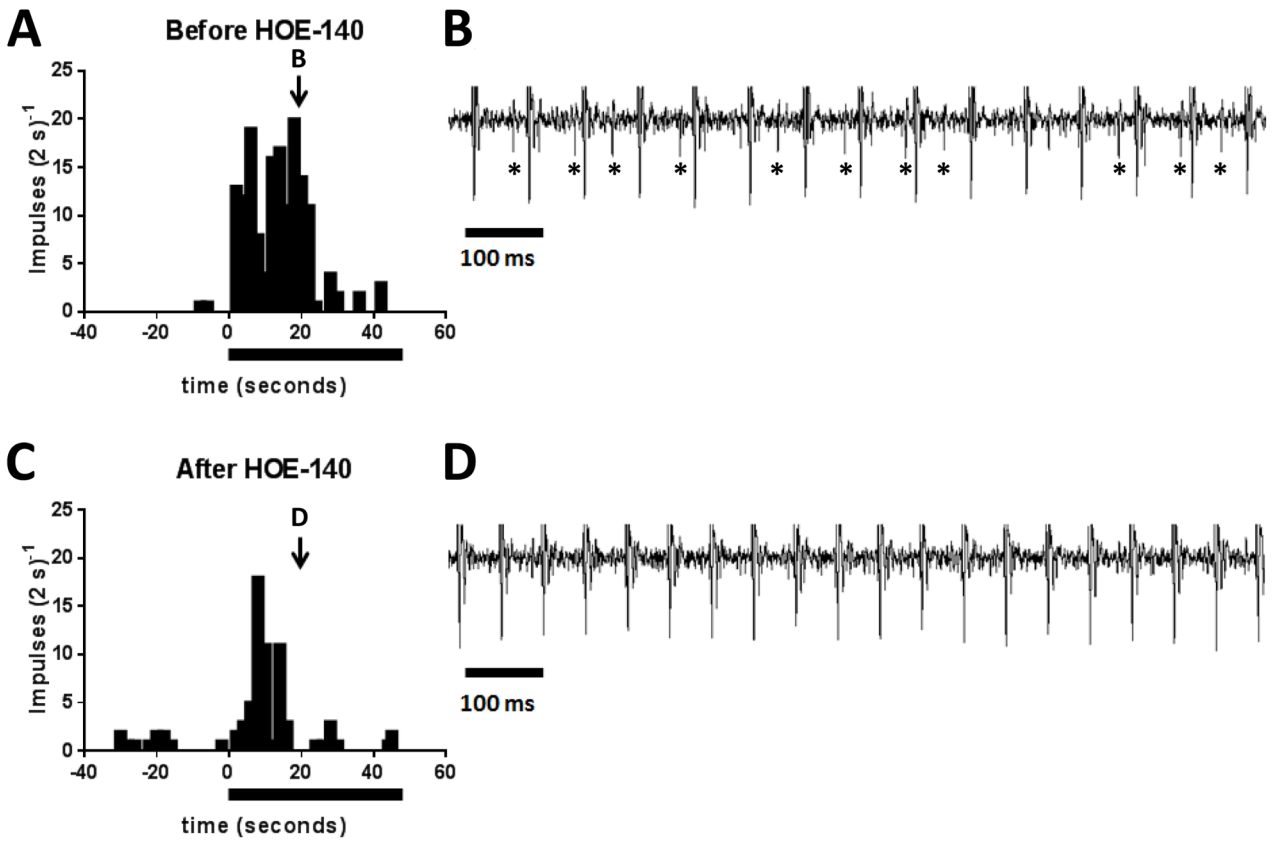

Figure 2.

The effect of HOE 140 (40μg/kg) on the responses to static contraction by a group III afferent (conduction velocity: 4.2 m/s). A and C plot the discharge of the group III afferent before, during, and after static contraction, which is signified by the filled horizontal bar. B and D show the recording of the afferent's discharge at the same time points of the contraction period and is depicted by the arrow and corresponding letter in A and C. Note that the large vertical, equally spaced lines in B and D are stimulus artifact induced by electrical stimulation of the ventral roots. In B the ventral roots were stimulated at 15 Hz, whereas in D the ventral roots were stimulated at 20 Hz. The increase in frequency was necessitated to match tension development. Asterisks (*) signify impulses generated by the group III afferent.

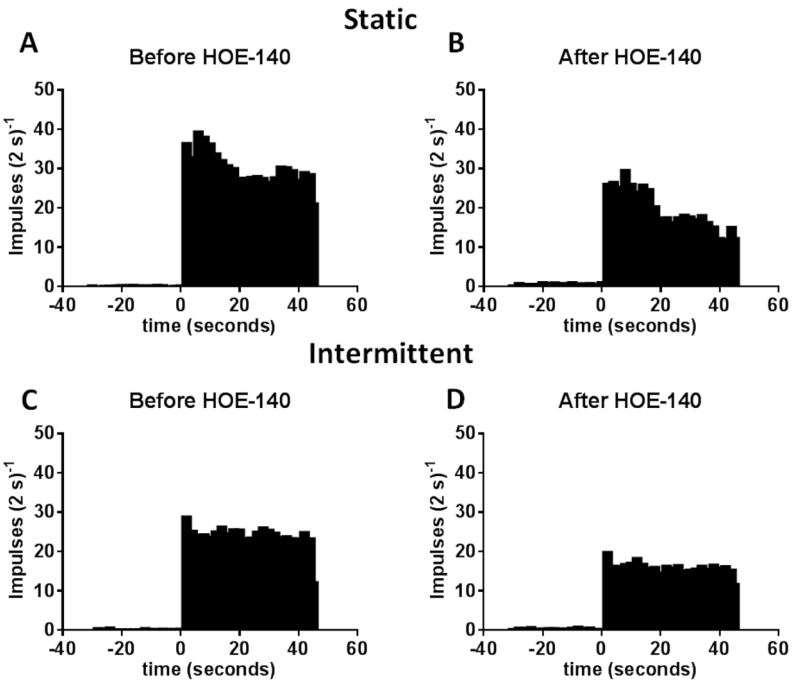

Figure 3.

A and B represent cumulative plots of the effects of HOE 140 (40 μg/kg) on the discharge of the 12 of the 14 group III afferents whose responses to static contraction were attenuated by B_2 receptor blockade. Likewise C and D represent cumulative plots of the effects of HOE 140 (40 μg/kg) on the discharge of the 12 of the 16 group III afferents whose responses to intermittent contraction were attenuated by B_2 receptor blockade. Note that the contraction period started at time zero and continued for 45 seconds.