

Studies using pharmacological blockade of muscle afferents provide new insights into the neurophysiology of perceived exertion

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17 Muscle contractions produce mechanical and chemical stimulation of both thinly
18 myelinated (group III) and unmyelinated (group IV) muscle afferents, increasing their
19 discharge towards the central nervous system. This afferent feedback is a key determinant in
20 the regulation of human endurance performance as it stimulates cardiovascular responses to
21 the exercise (i.e. “exercise pressor reflex”). While the role of group III-IV muscle afferents in
22 the regulation of cardiovascular responses to the exercise in healthy subjects is well known,
23 its role in the regulation of cardiovascular responses to the exercise in pathological population
24 remains poorly understood. In a recent article in *The Journal of Physiology*, Barbosa *et al.*
25 (2016) demonstrated that feedback from group III-IV muscle afferents contributes to the
26 exaggerated blood pressure response to cycling exercise in hypertensive men. To do so, the
27 authors attenuated the “exercise pressor reflex” by pharmacological blockade of muscle
28 afferent feedback. The spinal blockade of feedback from group III-IV muscle afferents in
29 hypertensive men induced a reduction in blood pressure during cycling, bringing blood
30 pressure values to a similar level to that of normotensive men. Interestingly, by monitoring
31 rating of perceived exertion (RPE) during cycling exercise with or without feedback from
32 group III-IV muscle afferents, the authors also significantly contributed to increase the
33 knowledge on the neurophysiology of perceived exertion. Namely, the authors reported that
34 RPE was similar in hypertensive subjects with or without pharmacological blockade of
35 muscle afferents (see p.719, paragraph “Responses to cycling”).

36 Perceived exertion, also known as perception of effort or sense of effort, is defined as
37 “*the conscious sensation of how hard, heavy and strenuous a physical task is*” (de Morree &
38 Marcora, 2015). This perception: i) provides information on the intensity of the exercise, ii) is
39 well used by clinicians to prescribe and monitor exercise during a rehabilitation program, iii)
40 strongly influences the self-regulation of human behaviour and iv) is one of the main features
41 of fatigue experienced by pathological populations. Despite its importance for researchers and

42 clinicians, to date, no consensus exists on the sensory signal(s) generating perceived exertion.
43 It is well accepted that the corollary discharge associated with the central motor command
44 constitutes, in part at least, the sensory signal producing the perception of effort. However,
45 there is an existing debate on the possibility that group III-IV muscle afferents could also
46 contribute to the sensory signal involved in the generation of perception of effort.

47 As performed in the recent study of Barbosa *et al.* (2016), one of the strongest
48 experimental manipulations that can be used to test the causal relation between group III-IV
49 muscle afferents and perceived effort is the pharmacological blockade of muscle afferent
50 feedback. Indeed, pharmacologically reducing the amount of muscle afferent feedback
51 integrated by the central nervous system, while monitoring RPE during a physical task,
52 provides a unique opportunity for testing the hypothesis that feedback from group III-IV
53 muscle afferents generates perception of effort. Such experimental manipulation has
54 previously been performed during static (Mitchell *et al.*, 1989; Smith *et al.*, 2003) and
55 dynamic (Fernandes *et al.*, 1990; Smith *et al.*, 2003) exercises. However, as RPE was not the
56 main outcome of these studies, the RPE results have not been thoroughly discussed. This
57 Journal Club aims at putting the results of Barbosa *et al.* (2016) in perspective with those of
58 other similar studies published in The Journal of Physiology (Mitchell *et al.*, 1989; Fernandes
59 *et al.*, 1990; Smith *et al.*, 2003) to get a better insight into the neurophysiology of perceived
60 exertion. Since perception of effort differs from perception of discomfort, pain and other
61 exercise-related sensations, we discuss the RPE results of studies that did not explicitly
62 associate discomfort and effort. In the studies cited below, authors used the 6-20 Borg scale to
63 quantify “*the intensity of effort*” exerted during dynamic and static exercise.

64 *Dynamic exercise.* Similarly to Barbosa *et al.* (2016), other studies reported no effect
65 of pharmacological blockade of muscle afferents on perceived exertion during dynamic
66 exercises. Of particular interest is the study of Fernandes *et al.* (1990) demonstrating that

67 epidural anaesthesia (i.e. using lidocaine) does not reduce perceived exertion during
68 submaximal cycling at a fixed workload corresponding to 57% of maximum oxygen uptake,
69 but in contrast increased it (due to lidocaine-induced muscle weakness and compensatory
70 increase in central motor command). Another key finding of this study is that at a given
71 oxygen uptake, RPE was similar with or without epidural anaesthesia (see Fig.1A). The lack
72 of effect of pharmacological blockade of muscle afferents on RPE during dynamic exercise
73 has also been shown by Smith *et al.* (2003). In this study, the authors demonstrated that
74 cycling during 7 min at 30% of maximal work rate with or without epidural anaesthesia does
75 not influence perception of effort. Therefore, the aforementioned studies provide strong
76 experimental evidence suggesting that removing feedback from group III-IV muscle afferents
77 does not reduce perceived exertion during dynamic exercise.

78 *Static exercise.* In 1989, Mitchell *et al.* (1989) performed one-leg static contractions of
79 the knee extensors with or without epidural anaesthesia (i.e. using lidocaine). Due to
80 lidocaine-induced muscle weakness, the effort required to produce the same absolute force
81 was higher after epidural anaesthesia. As explained by the authors, muscle weakness induced
82 by lidocaine injection leads the subjects to produce a greater central motor command to
83 maintain the same absolute force, consequently increasing perceived exertion. Interestingly,
84 when the reduction in force production capacity was taken into account and subjects were
85 asked to produce the same relative force (i.e. same central motor command), subjects
86 perceived the same effort with or without feedback from group III-IV muscle afferents. In
87 2003, Smith *et al.* (2003) also found that subjects reported the same RPE during static
88 contraction of the dominant leg performed with or without epidural anaesthesia (Fig 1B).
89 Similarly to dynamic exercises, it seems that removing feedback from group III-IV muscle
90 afferents does not reduce perceived exertion during static exercise.

91

PLEASE INSERT FIGURE 1 HERE

92 By integrating experimental evidence gathered during dynamic and static exercises,
93 the present Journal Club highlights that pharmacological blockade of muscle afferents does
94 not alter perceived exertion. Therefore, these results support the hypothesis that perceived
95 exertion is generated by central processing of the corollary discharge (associated to the central
96 motor command), and not by feedback from group III-IV muscle afferents. However, it is
97 important to note that even if feedback from group III-IV muscle afferents does not generate
98 perceived exertion (i.e. is not the sensory signal), this feedback may still indirectly impact
99 perceived exertion via its complex interaction with motor control and cardiovascular
100 responses to the exercise. This is indeed supported by the contrasted results of two
101 experimental studies investigating the impact of epidural anaesthesia (i.e. using fentanyl) on
102 endurance performance in competitive cyclists (Amann *et al.*, 2009; Amann *et al.*, 2011). In
103 these studies, pharmacological blockade of muscle afferent feedback led to increased central
104 motor drive (measured with EMG) that induced an exacerbated power output that would
105 otherwise be chosen by the subject (when performance was measured during self-paced
106 exercise; Amann *et al.*, 2009), itself leading to a faster O₂ consumption by the working
107 muscles and to a 21% performance decrement (time to exhaustion at 80% of peak power
108 output; Amann *et al.*, 2011) or no change in performance (5 Km time trial; Amann *et al.*,
109 2009).

110 Current theories in motor control propose that afferent feedback is continuously
111 monitored and integrated by the central nervous system so as to optimize the planning and
112 control of voluntary movements. Notably, echoing humans' well-known laziness,
113 computational studies emphasize the importance of effort-related optimization processes as a
114 guiding principle tailoring the production of motor patterns (Selinger *et al.*, 2015). For
115 example, by perturbing legs biomechanics of walking subjects, Selinger *et al.* (2015) recently
116 showed that humans continuously adjust stepping frequency in such a way that some effort-

117 related criterion is minimized. Also, not only the tailoring of motor patterns but also whether
118 or not one would engage in physical exercise is thought to be under the influence of effort-
119 related central processes. As voluntary movements are inherently costly, it has been proposed
120 that decision-making (i.e. the process of choosing between different options) relies on a cost-
121 benefit comparison from which the option that entails the best trade-off is chosen over the
122 others. A newly published study suggests that obese people, compared to lean people, may be
123 characterized by an abnormal cost-benefit decision-making that under-values the reward
124 obtained from the engagement in physical exercise (Mathar *et al.*, 2016). Unexpectedly,
125 Mathar *et al.* (2016) demonstrated that obese individuals, compared to lean individuals, are
126 less willing to engage in physical effort to obtain high caloric sweet snack food rewards.

127 Given the outstanding societal challenge of inciting people to engage in physical
128 activity (for primary to tertiary disease prevention), the important role of effort-related central
129 processes in human volition warrants the absolute need for a fine understanding of the
130 complex neurophysiological mechanisms underlying perception of effort. Studies using
131 pharmacological blockade of muscle afferent feedback present strong interests for this matter.

132

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135

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171

172 **FIGURE**

173 Effect of pharmacological blockade of muscle afferents on rating of perceived exertion
174 (RPE) during dynamic (panel A, adapted from Fernandes *et al.*, 1990) and static (panel B,
175 adapted from Smith *et al.*, 2003) exercise.

