Endocannabinoids and Motor Behavior: CB1 Receptors Also Control Running Activity

El Manira and Kyriakatos recently highlighted the key influence of the central endocannabinoid system in motor behavior, including motor learning (5). This highly comprehensive review has detailed how and where CNS endocannabinoids, i.e., lipid molecules released on demand from the postsynaptic cell that then act in a retrograde manner on cannabinoid (CB) receptors located on the presynaptic cell (11), exert a tight influence on motor behaviors (5). Actually, El Manira and Kyriakatos propose that endocannabinoids are endowed with a stimulatory influence on locomotion by means of CB1 receptor-dependent modulation of excitability and short-/long-term synaptic plasticity in neocortical, striatal, cerebellar, and spinal cord networks (5). We wish to add that such a hypothesis, which is supported by a vast array of experimental data gathered in different animal species, may possibly extend to one particular form of motor behavior that was not addressed in the aforementioned review: namely voluntary running. Thus we have recently shown that male mice lacking CB1 receptors display decreased voluntary running when housed with a running wheel for several weeks compared with their wild-type littermates (4). Such a difference is accounted for by a decrease in the time spent running, which leads to a shorter distance covered each day [3–4 km in CB1 mutants as opposed to 5–6 km in wildtype mice (4)]. Mice are nocturnal animals and thus engage in motor activity during the dark phase of the nycthemeral cycle. A comparison of the daily patterns of running behavior (in mice offered running wheels) and locomotor activity (in mice housed without running wheels) reveals that the former, but not the latter, behavior is under the control of CB1 receptors (FIGURE 1). The observation that locomotor activity (as opposed to locomotor reactivity, e.g., to novel environments) is not affected by the absence of CB1 receptors is not new and has been documented in the past (6, 7). As concerns the control of running behavior by CB1 receptors, our most recent observations indicate that such a control is also detected when mice are offered restricted (3 h) availability to the wheels (Chaouloff F, Dubreucq S, Bellocchio L, Marsicano G, unpublished observations). In turn, this strongly suggests that these data gathered in mice may well extend to humans where regular exercise is performed through short (1–2 h), daily bouts of running. Because the human gene encoding for the CB1 receptor, namely CNR1, displays polymorphisms (2), it is tempting to propose that human genetic variations in the CNR1 gene may actually bear an impact on the adherence to running exercise programs.

Where and how CB1 receptors exert a tight control on running behavior is presently unknown. First, it should be acknowledged that running, although voluntary, may be an extremely complex behavior (13). As an illustration, rodent (as well as human) voluntary running has been considered a task with high rewarding consequences (13). The tight relationships between the endocannabinoid system and central reward processes (8) indicate the need to encompass the circuitry of reward in addition to that linked to motor control. Second, because CB1 receptors are present also in peripheral tissues, including adipose tissue, liver, and muscles (12), one needs to consider an energy metabolism-related hypothesis wherein peripheral receptors, either alone or in combination with CNS
receptors, influence running behavior. A third hypothesis, which does not exclude the former ones, relates to the control of motor programs by CNS endocannabinoids (5). In this context, it is relevant to mention here that a great majority of CB1 receptors is located on GABAergic neurons (e.g., medium spiny neurons) and interneurons (9). Indeed, El Manira and Kyriakatos have thoroughly illustrated in their review the key importance of such a population of CB1 receptors, especially that found in the spinal cord or in the basal ganglia, with respect to motor behaviors (5). Interestingly, a report has indicated that wheel-running in mice potentiates the CB1 receptor-dependent inhibitory control of striatal GABAergic, but not glutamatergic, transmission (3). These results, which indicate a close link between CB1 receptors located on GABAergic neurons and motor activity, may indeed extend to particular forms of motor tasks such as running. However, the hypothesis that CB1 receptors control voluntary running behavior through their modulation of GABAergic transmission should be taken with caution. The need for such caution is illustrated by recent data aimed at defining the role of the endocannabinoid system in drug addiction. The experiments to which the authors refer in this Letter were supported by NARSAD (2008 NARSAD Independent Investigator Award to G. Marsicano), la Fédération pour la Recherche sur le Cerveau, la Délégation Générale pour l’Armement du Ministère de la Défense (PhD grant support to S. Dubreucq), the AVENIR/INSM program (Fondation Bettencourt-Schueller), and the Aquitaine Region.

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References