available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainresrev

BRAIN RESEARCH REVIEWS

Review

Brain regions and genes affecting limb-clasping responses

R. Lalonde[a,*], C. Strazielle[b]

[a]Université de Rouen, Faculté des Sciences, Dépt. Psychologie, 76821 Mont-Saint-Aignan Cedex, France
[b]Université Henri Poincaré, Nancy I, Laboratoire de Nutrition Génétique et Exposition aux Risques Environnementaux, INSERM U954, Service de Microscopie Electronique, Faculté de Médecine, 54500 Vandoeuvre-les-Nancy, France

ARTICLE INFO

Article history:
Accepted 20 February 2011
Available online 25 February 2011

Keywords:
Pathological reflex
Clasping reflex
Bat-like posture
Cerebellum
Noradrenaline
Serotonin
Basal ganglia
Striatum
Alzheimer's disease
Genetically modified mice

ABSTRACT

Adult rodents picked up by the tail and slowly descending towards a horizontal surface extend all four limbs in anticipation of contact. Mouse mutants with pathologies in various brain regions and the spinal cord display instead a flexion response, often characterized by paw-clasping and a bat-like posture. These phenotypes are observed in mice with lesions in cerebellum, basal ganglia, and neocortex, as well as transgenic models of Alzheimer's disease. The underlying mechanism appears to include cerebello-cortico-reticular and cortico-striato-pallido-reticular pathways, possibly triggered by changes in noradrenaline and serotonin transmission.

Contents

* *Corresponding author*. Fax: +33 02 35 14 63 49.
E-mail address: robert.lalonde@univ-rouen.fr (R. Lalonde).

0165-0173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainresrev.2011.02.005

1. Paw-clasping in normal mice

When adult rodents are picked up by the tail and slowly lowered towards a horizontal surface, they extend all four paws in anticipation of contact with the ground (Fig. 1a). This response may be triggered by either visual or tactile stimuli, the latter with the vibrissae or paw (Irwin, 1968). Visual stimuli are usually sufficient to initiate the placing response, but, in some cases, depending on genetic background and age, even normal mice extend their paws only at the moment they touch the ground, due to retinal deficiencies found in some strains and the debilitating effect of aging. This aspect has been insufficiently examined, since, to our knowledge, no report exits on the influence of the most commonly used mouse strains on the placing response and how this response alters with aging. In addition to sensory pathways, the placing reflex depends on spinal motor pathways responsible for moving fore- and hindlimbs.

The visual placing response in rodents can only appear after eye opening during the second postnatal week. However, the tactile placing response can be evaluated throughout the postnatal period. In normal mice, the limb-clasping response is progressively converted to extension prior to weaning (Takahashi et al., 2010). Thus, the neural pathways responsible for limb extension mature very quickly to the adult form. Instead of limb extension, limb flexion occurs in early developmental stages, sometimes with clasping of fore- or hindpaws, as seen in brain-lesioned mice (Fig. 1b), sometimes with all four limbs tucked towards the axial part of the body in a bat-like posture (Fig. 1 c), hindpaw clasping presented in the form of a video by Guyenet et al. (2010). These anomalies are distinct from the normal response of grasping a bar, testable as early as postnatal day 3, and impaired in the *Reln*^{rl} (*reeler*) cerebellar mutant on postnatal day 11 (Laviola et al., 2006).

Even in normal adult mice, paw-clasping may occur instead of limb extension. The often used C57BL/6 mouse has good visual acuity relative to many other mouse strains and usually displays the visual placing response. However, up to 10% of C57B6/SJL hybrids displayed hindlimb clasping, presumably as a consequence of "abnormal" genes on the SJL background (Lalonde et al., 2003). But no hindlimb clasping was observed in B6C3 hybrids, indicating that the C3H background possesses no abnormal gene of this kind (Lalonde et al., 2004, 2005a). In this ignored branch of research, a high throughput analysis of mouse genetics is needed, though easily feasible, since this response can be assessed even by relatively untrained technicians, information likely to be useful in screening neurological mutants.

The purpose of the present review is to summarize findings of mouse mutations affecting the placing reflex, regarding not only the functional effects of genes but also sensorimotor regions underlying normal and abnormal motor responses. Table 1 summarizes murine mutants with spinal and brain lesions exhibiting the abnormal paw-clasping response.

2. Spinal cord

Massive destruction of α-motoneurons prevents any possibility of responding. However, abnormal responses may occur in mice with ventral spinal damage prior to paralysis. This is the case in mice with the spontaneous *mnd* (motor neuron damage) mutation of the *Cln8*'gene, encoding ceroid-lipofuscinosis neuronal 8, eventually paralyzed as a result of α-motoneuron degeneration (Messer and Flaherty, 1986). Prior to paralysis, the *Cln8*^{mnd} mutants display limb flexion, perhaps due to dysfunction at the spinal level. But since *Cln8* mRNA is highly expressed in adult neocortex and other brain regions (Lonka et al., 2005), the abnormal phenotype may also be due to brain dysfunction, though neuropathologic analyses reveal mainly spinal damage.

A role for dysfunctional α-motoneurons in pathological reflexes is supported by observing hindpaw clasping and the bat-like posture in transgenic mice expressing full-length mutated *Ar* (androgen receptor), with α-motoneuron degeneration but without volumetric changes in cerebellum and striatum (McManamny et al., 2002), brain areas presumed to be involved in the same neurologic responses (see below). Moreover, hindpaw clasping provoked by contact with a glass surface, though not in the usual air suspension procedure, was observed in null mutants of *Smn2* (survival motoneuron type 2) with inserted human *SMN2* and *SMNdelta7* variants to prevent embryonic lethality and mitigate spinal and brainstem motoneuron loss (El-Khodor et al., 2008). Hindpaw clasping was also detected in the *NEFL*^{P22S} mutant model of Charcot-Marie-Tooth disease type 2E, mutated for neurofilament of light molecular weight and characterized by axonopathy of spinal pathways (Dequen et al., 2010). In addition, fore- and hindpaw clasping

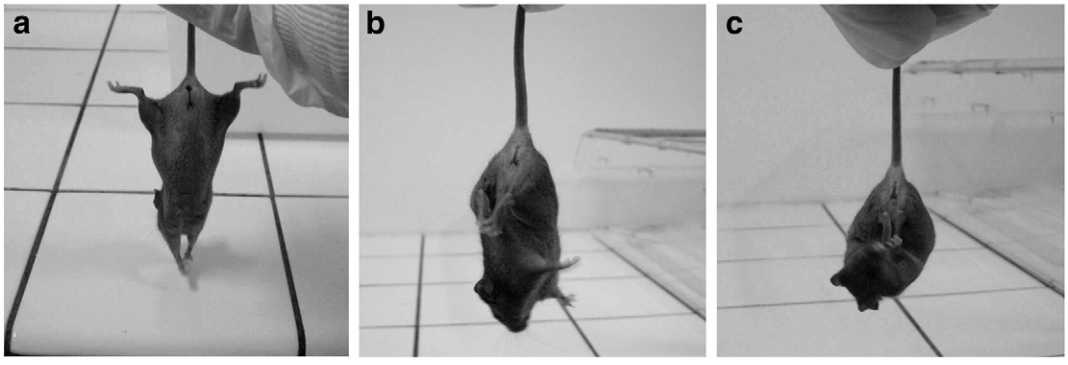

Fig. 1 – Limb extension in normal mice (a), whereas in *Dab1*^{scm} (*scrambler*) mutants with cell ectopias and degeneration in cerebellar cortex there is paw-clasping (b) and a bat-like posture (c).