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Behavioral phenotyping of mouse grooming and barbering

Peter Canavello, Jonathan Cachat, Allan V. Kalueff*

*Department of Pharmacology, Tulane University Medical School, 1430 Tulane Ave., New Orleans, LA 70112, USA

Corresponding author:

Allan V. Kalueff, PhD

Depart. of Pharmacology, RM 3733

Tulane University Medical School, 1430 Tulane Ave, SL-83

New Orleans, LA, 70112 USA

Tel. 1-504-988-3357   Fax. 1-504-988-5283

E-mail: avkalueff@gmail.com

ABBREVIATIONS:

GABA – γ-amino butyric acid

MGI – Mouse Genome Informatics Database

MPD – Mouse Phenome Database

OCD - Obsessive-compulsive disorder

INTRODUCTION

Grooming is an ancient behavior that is represented (with a striking homology) across most vertebrate species, including humans (Fentress, 1977; Sachs, 1988; Young and Thiessen, 1991). Its biological functions include care of body surface, removal of ectoparasites, thermoregulation, chemo-communication, sensory stimulation of skin, displacement, de-arousal, maternal and social interaction (Spruijt et al., 1992; Ferkin et al., 1996; Ferkin and Leonard, 2005).

Both self- and heterogrooming behaviors are commonly seen in wild and laboratory rodents (Bolles, 1960; van Abeelen, 1966; Dunn et al., 1987; Berntson et al., 1988; Sachs, 1988). Self-grooming is common in mice, representing >15% of all waking time, and, after sleep, is the most frequently observed activity in their repertoire. It can be induced in animals by various factors, such as novelty, misting with water, swimming, exposure to predators or their odors, and pain (File et al., 1988; Kalueff et al., 2004a; Burne et al., 2006; Boccalon et al., 2006). It is also often seen during pregnancy (Harvey and Mann, 1988), as a "transitional element" between rest and exploration (Fentress, 1988), or as a part of sexual behavior (Sachs, 1988).

Many endogenous substances, including neuromediators such as dopamine, γ-aminobutyric acid (GABA), serotonin, and hormones (adrenocorticotropin, vasopressin, oxytocin, prolactin, substance P, somatostatin, bombesin, corticotropin releasing hormone, opioids, cholecystokinin; Gorris et al., 1981; Hall et al., 1985; Dunn et al., 1987, 1988; Bertolini et al., 1988; Ukai et al., 1989; Spruijt et al., 1992) as well as multiple brain regions (especially basal ganglia and hypothalamus) are involved in the regulation of rodent self-grooming (Berntson et al., 1988; Roeling et al., 1993; Kruk et al., 1998; Aldridge et al., 2004). Various psychotropic drugs (Dunn, 1988; File et al., 1988; Barros et al., 1994; Kalueff and Tuohimaa,

2005c; Yalcin et al., 2005; Audet et al., 2006) also affect rodent grooming, collectively making its analysis a useful tool in behavioral neuroscience.

In addition to grooming, behavior-associated hair loss (over-grooming, or barbering [in humans - trichotillomania, which afflicts approximately 1% of the population]) has long been observed in many species (Hauchka, 1952; Sarna et al., 2000; Honess et al., 2005; Reinhardt, 2005), suggesting that both behaviors may have a common evolutionary origin. Described in the rodent literature as whisker/hair or fur trimming, de-whiskering, or the Dalila effect, barbering is particularly common in laboratory mice (Van de Weerd et al., 1992; Garner et al., 2004ab). Mouse barbering includes plucking of fur or whiskers from cage-mates (hetero-barbering) or oneself (self-barbering) (Long, 1972, Strozik and Festing, 1981; Kurien et al., 2005).

Mounting data indicate that mouse barbering may be a form of dominant behavior and a strong indicator of social hierarchy (Long, 1972; Sarna et al., 2000). In groups of mice, there will often be one with unbarbered whiskers, playing a dominant role in the cage (Strozik and Festing, 1981, Carruthers et al., 1997; Sarna et al., 2000; Kalueff et al., 2006). Whisker removal occurs even if the mice are separated by wire mesh, indicating that both animals co-operate in this behavior (Van den Broek et al., 1993). Several husbandry factors have been reported to affect mouse barbering (e.g., diet, weaning age and enrichment; Myers, 1997 and De Luca, 1997), suggesting that it may represent a stress-evoked response (e.g., coping with inappropriate housing; Van den Broek et al., 1993), or a pathological, compulsive-like behavior (Garner et al., 2004ab). Given its frequent occurrence in mice, barbering appears to be an important part of their behavioral repertoire. This Chapter will focus on behavioral phenotyping of hetero-barbering and self-grooming in mice, the species that best represents each of these behaviors.

PHENOTYPING OF SELF-GROOMING

Mouse grooming appears in early ontogenesis, confirming the evolutionarily ancient age of this behavior (Golani and Fentress, 1985; Sachs, 1988; Sviderskaia and Dmitrieva, 1993). Usually more frequent in the home cage (Berridge et al., 2005), self-grooming is also seen in stressful situations, such as novelty-based anxiety tests (e.g., elevated plus maze, open field and holeboard tests), implying that this behavior is not only important to assess, but can also interfere with the primary behavior being assessed, thus becoming a confounding factor, if neglected.

Nevertheless, in many studies this behavior has received little attention. Surprisingly, there is no grooming data in the extensive Mouse Phenome Database (MPD), nor in recent comprehensive studies (Rogers et al., 1999; Tang et al., 2002; Voikar et al., 2001, 2004). Some authors assessed several grooming patterns but reported only one global behavioral score (e.g., Dunn et al., 1987). Others compared different strains but analyzed only cumulative scores (Cabib and Bonaventura, 1997; Nyberg et al., 2003; Leppanen et al., 2006), or even combined grooming data in "overall activity scores" with horizontal and vertical exploration (e.g., Wirth-Dzieciolowska et al., 2005). Still other studies assessed grooming indices in different strains cursorily among other measures, mostly including gross activity characteristics such as the latency, frequency and duration of grooming (e.g., Dell'Omo et al., 1994; Rodgers et al., 2002; Voikar et al., 2005),.

There is a growing understanding, however, that quantitative measures alone may be insufficient for correct interpretation and analysis of mouse grooming data (Fentress, 1988; Kalueff and Tuohimaa, 2004a). Rodent grooming is a complex, ethologically rich ritual, which normally proceeds in a cephalocaudal direction and consists of several stages: licking the paws, washing movements over the head, body fur licking and tail/genital cleaning (Spruijt et al., 1992; Berridge et al., 2005) [Fig. 1]. Dissectible at a number of levels, ranging from individual organ

kinematics (Kobayashi et al., 2002) to sequencing and habituation in grooming patterns and their association with non-grooming behaviors (Fentress, 1988; Cabib et al., 1990; Berridge et al., 2005), such complex patterned structure is particularly attractive for behavioral phenotyping. Importantly, this approach can be used not only to assess "normal" mouse behaviors and their patterning, but also as a source for ethologically-oriented experimental models of human stereotypic behavioral disorders. For example, the utility of grooming assessment has recently been indicated for the development of mouse models of obsessive-compulsive disorder (OCD) and Tourette syndrome (Berridge et al., 2005; Albin and Mink, 2006). Consistent with this, psychotropic drugs such as m-CPP, a serotonin receptor 2 agonist that exacerbates OCD in clinical patients (Pigott et al., 1993), have been reported to elicit robust rodent grooming (Graf et al., 2003). These findings suggest that grooming phenotyping may also hold potential for extensive use in behavioral pharmacology (also see Kalueff and Tuohimaa, 2005c for discussion). Table 1 summarizes methodological approaches to mouse grooming phenotyping.
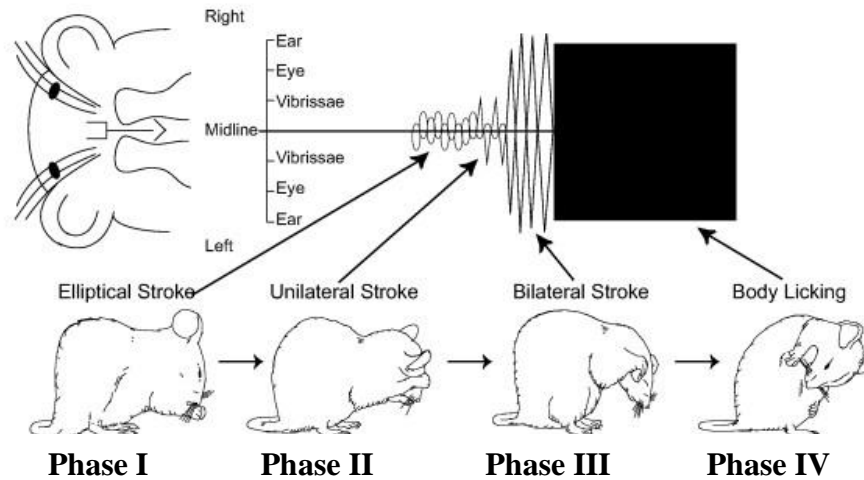
Figure 1. Prototypical syntactic grooming chain pattern in mice (adapted from Berridge et al., 2005, with permission). Phase I*:* series of ellipse-shaped strokes tightly around the nose (paw, nose grooming). Phase II*:* series of unilateral strokes (each made by one paw) that reach up the mystacial vibrissae to below the eye (face grooming). Phase III*:* series of bilateral strokes made by both paws simultaneously. Paws reach back and upwards, ascending usually high enough to pass over the ears (head grooming). Phase IV*:* body licking, preceded by postural cephalocaudal transition from paw/head grooming to body grooming.

Table 1. Methodological approaches to mouse grooming

General cumulative measures
• The latency to onset, the duration and the number of grooming episodes (bouts).
• The following patterns can be recorded for each bout: paw licking; nose/face grooming; head washing; body and leg grooming/scratching; tail/genitals grooming
• Additional cumulative indices: the average duration of a single grooming bout, total number of transitions between grooming stages and average number of transitions per bout
Patterning
• The percentages of incorrect transitions, as well as interrupted and incomplete grooming bouts (see details in: Kalueff et al., 2005a; Kalueff and Tuohimaa, 2004b, 2005a-c)
Regional distribution of grooming
• Can be assessed as directed to the following five anatomic areas: forepaws, head, body, hind legs and tail/genitals. Rostral grooming includes forepaw (preliminary rostral grooming) and head grooming. Body, legs and tail/genital grooming can be considered as caudal grooming.
• Each bout can be categorized as being directed to (i) multiple regions or (ii) a single region, and the percentages of grooming bouts and of time spent grooming can be calculated for both categories (see details in: Dunn et al., 1987; Kalueff and Tuohimaa, 2004b, 2005a-c)
Additional useful indices of grooming
• Probability of chain initiation (frequency of chain initiation per minute of grooming time)
• Probability of pattern completion once initiated (see Berridge and Aldridge, 2000 for the rat protocol, which can be easily adapted to use with mice)

Interesting data continue to accumulate on the behavioral genetics of mouse grooming. Van Abeelen (1963abc) found that increased grooming is associated with the *pink-eyed dilution* (*p*) and *brown coat color* (*b*) loci on chromosomes 7 and 4, respectively[1]. Allelic variations in p locus have been found in many strains of laboratory mice (Brilliant et al., 1994), and may be associated with some strain differences in self-grooming behavior. On the other hand, some data suggest that both *p* and *b* loci are associated with increased anxiety (Clement et al., 1994; Clement and Chapouthier, 1998), implying interaction between "grooming" and "anxiety" domains at both genetic and behavioral levels. In line with this, ABP/Le and C57BL/6 mice demonstrated association of increased novelty-induced grooming with autosomal *short ear* (*se*) locus on chromosome 9 (Clement et al., 1994), also implicated in mouse avoidance behavior (see van Abeelen, 1966 for details). This study also confirmed the role of *p* locus, suggesting multi-locus contributions to grooming phenotype in mice. Moreover, although *se* locus has also been linked to anxiety (Clement et al., 2002), it is crucial for normal growth and patterning of skeletal structures (Kingsley et al., 1992), implying a possible musculoskeletal component. Clearly, further studies are needed to map grooming to specific genes and chromosomes in mice and other rodents (e.g., Fernandez-Teruel et al., 2002; Flint, 2004).

Many neurobehavioral studies have considered strain differences in mouse grooming (Table 2). For example, Streng (1971) tested BALB/cIbg, C57BL/6Ibg, A/Ibg and DBA/2Ibg mice in the open field, analyzing their cumulative grooming scores and reporting significant time effect (grooming increase over a test period, observed in all strains) and time x strain effects.

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[1] The p locus (28.0 cM) on chromosome 7 is close to a cluster of GABAergic genes (28.2-28.6 cM) encoding $\gamma 3$, $\alpha 5$ and $\beta 3$ subunits of GABA-A receptors (Culiat et al., 1994; also MGI). GABAergic system is known to regulate both grooming and emotional behaviours, and it is possible that these subunits play a role in grooming phenotypes (also see tendency to a lower grooming in mice selectively bred for sensitivity to β-carboline seizures in: Suaudeau et al., 2000).

Schoots et al. (1978) assessed grooming frequency and duration in C57BL/6 and DBA/2 mice, reporting more grooming in DBA/2 strain regardless of treatment (i.e., after saline injection or zinc-induced peripheral anosmia). Clement et al. (1994) noted that ABP/Le mice (carrying homozygous recessive genes *se, p* and *b*) groomed in the open field significantly more than less anxious C57BL/6, while F1 ABP/Le-C57BL/6 mice groomed more than F1 C57BL/6-ABP/Le (suggesting possible maternal effects). Another group analyzed genetic architectures of mouse novelty grooming, reporting ambidirectional dominance (for both frequency and duration), albeit rather weak, since it disappeared in the 5x5 diallele cross (Crusio and van Abeelen, 1986, 1987; Crusio et al., 1989).

Table 2. Examples of strain differences in mouse grooming behavior

Strain differences	References
Frequency	
DBA/2J, F1 [C57BL/6J-DBA/2J] > C57BL/6J	Van Abeelen, 1966
A/Ibg, BALB/cIbg > DBA/2Ibg, C57BL/6Ibg	Streng, 1971
DBA/2J = CPB-K-Nmg = C3H/St = C57BL/6J	Crusio and van Abeelen, 1986
FVB/N = C57BL/6J	Mineur and Crusio, 2002
BALB/c = 129S1 = NMRI	Kalueff and Tuohimaa, 2005b
C57BL/6J > 129S1	Kalueff and Tuohimaa, 2004b
C57BL/6 = DBA/2	Cabib and Bonaventura, 1997
Duration	
DBA/2J > CPB-K-Nmg > C3H/St, C57BL/6J	Crusio and van Abeelen, 1986
C57BL/6J > FVB/N	Mineur and Crusio, 2002
C57BL/6J > BALB/cByJ	Ducottet and Belzung, 2004

C57BL/6J > 129S1	Kalueff and Tuohimaa, 2004b
BALB/c > 129S1, NMRI	Kalueff and Tuohimaa, 2005b

There were also different baseline levels of sweet water spray-evoked grooming in C57BL/6J and BALB/cByJ mice markedly different in their emotionality (Table 2), whereas reduced grooming duration was seen in stressed (vs. non-stressed) BALB/cByJ mice, compared to "resistant" C57BL/6J grooming (Ducottet and Belzung, 2004). Voikar et al. (2005) examined C57BL/6JOlaHsd and DBA/2OlaHsd mice, reporting significant strain effect on grooming in the elevated plus maze for both socially and single-housed mice (C57: ↓ duration, ↑ latency), and in single-housed mice in the Y-maze (C57: ↑ latency). In contrast, they found no strain effect on grooming duration in the Y-maze and reported a housing effect (↑ latency) in all four groups.

Rodgers et al. (2002) compared C57BL/6 and some 129 substrains, reporting lower light-dark grooming in 129SvEm (tendency) and 129SvHsD (significant decrease); similar results were seen for 129S1 mice in the social interaction (Hossain et al., 2004) and novelty- or water-evoked grooming tests (Kalueff and Tuohimaa, 2004a). Grooming scores rose in C57BL/6J mice during the dark (vs. the light) phase, but remained very low in 129S1 and F1 (C57BL/6J-129S1) mice (Hossain et al., 2004), negating possible maternal C57 influences. Mineur and Crusio (2002) compared open field behaviors of FVB/N and C57BL/6J strains, noting similar frequency but marked strain differences in the duration of grooming (Table 2). This again confirms that grooming indices, such as frequency and duration, may vary independently in different mouse strains, and therefore merit careful assessment in detail. Interestingly, grooming activity in this study did not correlate with open field horizontal and vertical activity (FVB/N > C57), suggesting that grooming activity represents a separate dimension in the structure of mouse behavior.

In a recent study (Kalueff and Tuohimaa, 2005b), the latency to start grooming was not statistically different in three mouse strains, although NMRI mice showed a clear tendency toward earlier onset of grooming, compared to both 129S1 and BALB/c strains (Table 2). This group also found no clear correlation between grooming activity measures and anxiety - with anxious strains showing both high (BALB/c) and low (129S1) grooming profiles, and non-anxious mice showing moderate-to-high grooming profiles (NMRI, C57BL/6) (Kalueff and Tuohimaa, 2004b, 2005b). Analyzing grooming in 129S1 mice and their F1 hybrids (129S1-C57BL/6, 129S1-BALB/c, 129S1-NMRI) in the open field test, they also (unpublished data; in line with Hossain et al., 2004) found more bouts in NMRI- and BALB/c-derived, than in 129S1 and C57-derived F1 mice (both displaying similar low-grooming phenotype). In contrast, BALB/c and NMRI mice (regardless of 129 maternal influences) seem to increase grooming activity in F1 progeny, resembling high-grooming phenotypes of their parents (Kalueff et al., 2005b).

More recently, Yalcin et al. (2008) performed a study combining the unpredictable chronic mild stress (UCMS) paradigm with administration of four different antidepressant drugs in both outbred Swiss and BALB/c mice. While BALB/c cohorts showed significantly reduced grooming under all treatments (including vehicle), Swiss mice under several treatments (vehicle, desipramine, maprotiline) groomed more frequently than non-stressed controls, though results in the latter strain were not significant. Another study (Avgustinovich et al., 2007), comparing open field behaviors in C57BL/6J and CBA/Lac mice, reported an increase in the number of grooming bouts in stressed subjects of C57 strain background, but no such change in CBA/Lac groups.

Notably, while the literature on strain differences in grooming is vast, relatively few studies focused on its patterning aspect. Analysis of grooming behavioral microstructure in 129S1, C57BL/6, BALB/c and NMRI strains (Kalueff and Tuohimaa, 2004b, 2005b) showed

that 129S1 mice display significantly higher percentages of incorrect transitions and interrupted grooming bouts. However, these measures did not differ between 129S1 and F1 hybrid strain (unpublished data), suggesting that 129 genes, maternal influences (or both) may determine grooming patterning. Perhaps, the "quantity" and the "quality" (patterning) of mouse grooming may have different genetic determinants, underlining the need for further studies in behavioral genetics of mouse grooming and its sequencing.

Grooming responses vary across selectively bred mouse strains. For example, female mice of Turku Aggressive strain spent less time grooming during predatory aggression, compared to Turku Non-aggressive strain (Sandnabba, 1995). In contrast, anxious high-thigmotaxis strain (derived from Swiss albino outbred stock) produced fewer grooming bouts in the open field than did less anxious mice of the low-thigmotaxis strain (Leppanen and Ewalds-Kvist, 2005; Leppanen et al., 2006, 2008). There are also interesting cross-fostering data revealing similar grooming activity in both high- and low-thigmotaxis strains (Leppanen and Ewalds-Kvist, 2005; Leppanen et al., 2006), and implying that both genetic and epigenetic factors influence mouse grooming. Since grooming is regulated by numerous endogenous mediators and hormones, their strain-specific variation may lead to altered grooming phenotypes. In line with this suggestion, Krehbiel et al. (1986) studied the DeFries mice, and found strain differences in self-grooming (L1 > C1, H2) paralleled by altered catecholamine neurotransmission.

Robust alterations in grooming have also been reported in several mouse strains with spontaneously occurring mutations. For example, *Lurcher* mice display reduced grooming of forelimb, abdomen, back and hind limb, also showing less complex bouts (Strazielle and Lalonde, 1998). In contrast, *weaver* mice show a greater number, but shorter duration of grooming bouts, perform a higher proportion of smaller forelimb strokes and more incomplete

grooming sequences (Coscia and Fentress, 1993; Bolivar et al., 1996). *Jimpy* mice (Bolivar and Brown, 1994) spend less time grooming, whereas s*taggerer* mice show less grooming but unaltered patterning (Fentress, 1999)[2]. Finally, aberrant grooming has been reported in many transgenic and knockout mice (e.g., Greer and Capecchi, 2002; Kalueff et al., 2005), which are not the scope of this volume (see, however, Mouse Genome Informatics MGI Database for details).

MOUSE BARBERING PHENOTYPING

The fact that mouse barbering profiles do not correlate with altered self-grooming (Sarna et al., 2000) suggests that they represent distinct behavioral domains (see, however, some overlap between barbering and hetero-grooming in the same study). In general, there are several reasons why assessment of mouse barbering may be important for neurobehavioral research. First, like grooming, it is an interesting behavior per se, representing an essential part of mouse activity (Sarna et al., 2000; Whishaw et al., 2001). Also, since barbering usually affects whiskers (regarded as a crucial source of sensory input in rodents), and whisking represents an essential part of rodent behavioral repertoire, altered whisker status in mice due to barbering may affect other behaviors, including performance in tasks such as eating, copulation, predator evasion, and various social interactions.

Finally, barbering is particularly common in some strains, especially C57BL/6, A2G and NMRI mice (Long, 1972, Strozik and Festing, 1981, Jackson Laboratory, 1987; Sarna et al., 2000; Kalueff et al., 2006), suggesting a strong genetic component in this behavior (Hauchka, 1952, Militzer and Wecker, 1986, Van den Broek et al., 1993 and McElwee et al., 1999). As it stands, further in-depth ethological analyses will be necessary to understand in detail the

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[2] Interestingly, *staggerer* locus on mouse chromosome 9 (36.0 cM) is very close to *se* locus (42.0 cM), linked to mouse grooming in earlier studies (Clement et al., 1994), suggesting that this area may indeed be important for mouse grooming.

etiological and genetic nature of mouse barbering (Table 3). Furthermore, phenotyping of mouse barbering can also lead to ethologically-oriented experimental models of human behavioral disorders. Indeed, the utility of barbering assessment has recently been suggested for mouse models of trichotillomania (Garner et al., 2004ab, Kurien et al., 2005), although it may bear relevance to other OCD- and aggression-related behaviors as well.

Table 3. Assessment of mouse barbering behavior

- The following 5-point scale can be used to assess mouse barbering: 0 - no barbering; 1 - whisker removal or shortening; 2 - snout/face denuding; 3 - individual bald patches on head and body; 4 - multiple alopecic areas on head and/or body; 5 - severe alopecia including complete snout denuding and large alopecic areas on head and body.

- Hair loss shall be scored as barbering only if the hair lesion was non-puritic, there was no scarring or scabbing around the lesion, and the animal was otherwise in good health and the fur (where present) was in good conditions (Garner et al., 2004ab).

- The following parameters of barbering can be assessed: the number (%) of cages in which the barbering occurred; the average severity of barbering in each cage; and the percentages of barbers and barbered animals (of total animals of each strain).

- Barber animals can be easily identified as the single intact mouse in the cage (see Sarna et al., 2000; Garner et al., 2004ab for details).

- If necessary, self-barbering may be assessed in mice housed individually (to prevent hetero-barbering) for 3-4 weeks (see Kalueff et al., 2006 for details).

- Sometimes, excessive grooming in mice (e.g., Greer and Capecchi, 2002) may lead to pronounced barbering-like alopecia (homecage observations may be needed in such cases to distinguish between the two behaviors).

Overall, there is limited available data on the behavioral genetics of murine barbering. In regard to genetic mapping of mouse barbering, this scarcity of data currently hinders comprehensive genotypic analysis of barbering phenotypes across strains. There have been surprisingly few data comparing barbering behaviors in different strains and their overlaps. De Luca (1997) reported interesting effects of enrichment on mouse barbering but did not specify the strain (also see Kurien et al., 2005), while Sarna et al. (2000) examined barbering behavior in detail, but only in one (C57BL/6J) strain. In a series of recent experiments (Kalueff et al., 2006; also unpublished 2004-2005 data) we assessed barbering in several strains and their F1 progeny, revealing distinct domains, such as social dominance barbering in same-sex cages in C57BL/6J, A/J, 129S1 and NMRI (but not BALB/c) mice, sexual barbering (male by females) in breeding C57BL/6J, 129S1 and NMRI (but not BALB/c) mice, and maternal barbering (ventral fur removal by pups in lactating C57BL/6 and 129S1 dams), as well as whisker barbering by 129S1 mothers in their pups.

Fig. 2 shows the variety of mouse barbering styles in different strains. Notably, the percentage of hair-barbering varies widely from strain to strain. For example, the BALB/c mice never show barbering, in contrast to ~20% of C57BL/6 and A/J (Long, 1972; Landau et al., 2001), ~75% of A2G (Strozik and Festing, 1981), and ~80–100% of NMRI mice (Kalueff et al., 2006). Sarna et al. (2000) have recently reported that C57BL/6J mice may demonstrate individual "cutting styles". Our studies showed that mice also displayed consistent strain-specific cutting styles (Fig. 2: snout + whiskers: NMRI; head and/or back: C57BL/6; whiskers: A/J and 129S1; face: F1 C57-129SvJ), further supporting the behaviorally complex and multi-factorial nature of mouse barbering (also see similar data for C57BL/6J mice and whisker barbering in another (129S6) 129 strain: Holmes et al., 2002). Notably, several F1 hybrid strains - C57-129S1

or 129S1-C57, NMRI-129S1 or 129S1-NMRI - display barbering styles which appear to be a mixture of those of both parental strains, and do not seem to be affected by maternal influences (Kalueff et al., 2006; also unpublished data). In contrast, the lack of barbering in F1 hybrids derived from BALB/c strain suggests strong low-barbering effects in this strain, also independent of maternal influences. Finally, cross-fostering experiments with several strains showed that both genetic and epigenetic factors may contribute to mouse barbering, since it was observed in mice of non-barbering strains raised with barbering foster parents, as well as in barbering strains (BALB/cBy) raised by non-barbering C57Bl/6J foster parents (Carruthers et al., 1998).

Figure 2. Typical barbering patterns in different mouse strains. A – Social (dominant) barbering (from left to right) in inbred 129S1, C57BL/6J, A/J and outbred NMRI male mice. Note missing whiskers in 129S1 and A/J mice, "haircut-style" in C57BL/6J, and snout denuding in one NMRI mouse (indicated by arrow; barber is a bigger mouse with normal whisker). B – Social (dominant) barbering in several F1 hybrid strains: C57BL/6-129SvJ, C57BL/6-129S1 and 129S1-NMRI mice. C – maternal barbering: ventral hair loss due to barbering by suckling pups in 129S1 and C57BL/6 female mice (indicated by arrows), and barbering (whisker trimming) by lactating dams of their pups in 129S1 strain (note normal whiskers in the dam, half-short whiskers in pup I, and completely missing whiskers in pup II)

In general, barbering activity (NMRI, C57 > 129 >>> BALB) negatively correlated with overall strain aggressiveness (BALB >> 129, C57 >> NMRI), supporting the notion that barbering might emerge in mice as a behavioral adaptation to minimize potential aggression (Kalueff et al., 2006). Alternatively, it might appear as a result of an absence of complex behavior to parry hair plucking (Whishaw et al., 2001), although this seems less plausible. In addition, further studies are needed to assess the potential relation of barbering to overall activity levels and to carry out in-depth ethological analyses in different mouse strains.

On a relevant note, an assessment of behavioral phenotypes of non-barbering (in addition to barbering) strains may be another useful approach to behavioral genetics of mouse barbering. For example, over 800 BALB/c mice used in Carruthers et al. (1997, 1998) studies did not barber (see similar results in Kalueff et al., 2006). Strain differences in sociability (Brodkin et al., 2004; Sankoorikal et al., 2006) have been recently suggested to underline barbering phenotypes (Brodkin, 2006).This interesting hypothesis, if confirmed, may explain high intensity of barbering in "sociable" strains (such as C57Bl/6 mice) and poor barbering in "autistic" mouse strains, such as BALB/c. Thus, barbering emerges as an essential part of mouse social behavior, and its strain differences may reflect (or underlie) different aspects and strategies of animal socialization. The latter, in turn, may confound all other behavioral domains, implying that in-depth analyses of strain barbering phenotypes may be even more important than has been previously recognized.

Finally, aberrant barbering is often seen in various mutant mice (e.g., Holmes et al., 2002; see MGI for details), collectively representing an important behavioral phenotypic effect with multiple mechanisms, genetic influences, neural substrates, forms and contexts. It is of likely relevance, therefore, to human psychopathologies, like autism and OCD spectrum disorders, that are characterized by dysfunction in social interaction .

CONCLUSION

Overall, there are clearly potential benefits to in-depth mouse grooming and barbering phenotyping. First, it allows the assessment of strain differences in these behaviors per se. Second, as already mentioned, grooming activity, and especially its sequencing, may reflect strain differences in activity, anxiety and motor patterning, in addition to the existing methods of emotionality phenotyping. Third, given the sensitivity of mouse grooming and its sequencing to various pharmacological and physiological manipulations in different strains, ethologically-oriented analysis of grooming may be useful in pharmacogenetics and neurophysiology (e.g., for dissection of brain substrates involved in the regulation of behaviors). Finally, altered grooming and barbering profiles may indicate behavioral stereotypy (Kalueff and Tuohimaa, 2004a; Garner et al., 2004ab). Indeed, it has been suggested that stereotypies in animals may originate from their natural behavioral repertoire of displacement activity (Wurbel et al., 1998ab; Low, 2003). Therefore, profiling of grooming and barbering phenotypes may allow researchers to indirectly assess potential strain differences in "stereotypicity".

Taken together, ethological analyses of mouse grooming and barbering can be a rich source of information in behavioral neurogenetics. Understanding how mice spend >15% of their waking time will enable us to better understand their behavior in general. Clearly, more attention has to be paid to grooming and barbering indices, including standard mouse behavioral protocols (e.g., SHIRPA; Rogers et al., 1997, 1999) and behavioral analytical software (e.g., Ethovision). In addition, many published studies include data on C57BL/6J mice, and given its active high-grooming/high-barbering phenotype, this strain can be suggested as a reference strain for future studies focusing on different aspects of grooming behavior. The existing phenotype databases (e.g., MPD) may also benefit from the inclusion of systematic grooming and barbering profiles for different mouse strains. Providing more comprehensive coverage of mouse behavioral

phenotypes and offering clever ideas on how known grooming/barbering peculiarities may affect other behaviors in different mouse strains will assist researchers in correct data interpretation and selection of appropriate mouse models for their tests.

USEFUL WEB-RESOURCES

MPD, Mouse Phenome Database   http://www.jax.org/phenome

MGI, Mouse Genome Informatics Database http://www.informatics.jax.org/

Noldus Ethovision   http://www.noldus.com/site/doc200403002

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