

Selective Response of Medial Amygdala Subregions to Reproductive and Defensive Chemosignals from Conspecific and Heterospecific Species

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Abstract. In hamsters and inbred mice, pheromone-containing chemosensory signals originating from the animal's own species (conspecific) and other species (heterospecific) produce differential patterns of immediate early gene (IEG = Fos/ FRAs) expression in the medial amygdala. In males of both species, conspecific stimuli, regardless of gender or putative function, activated neurons in both anterior and posterior medial amygdala (MeA, MeP). With heterospecific stimuli, MeA was activated but MeP appeared to be suppressed. MeP neurons expressing GABA-receptor were selectively suppressed by heterospecific stimuli at the same time as the GABAergic caudal intercalated nucleus (ICNc) of the amygdala was activated, suggesting suppression of MeP by ICN. We propose that information on conspecific chemosignals with preprogrammed meaning (pheromones) is analyzed by MeP neurons, probably influenced by gonadal steroid status. Information about heterospecific stimuli that activate anterior medial amygdala via the vomeronasal organ appears to have restricted access to MeP. Signals from conspecific males that are potentially threatening elicit different patterns of activation in MeP than other conspecific signals. In hamsters, male flank gland secretion activates predominantly GABA-immunoreactive neurons and mainly in ventral MeP (MePv). Male mouse urine also activates predominantly MePv in mice. This region responds to predator odors in rats and is reported to do so in mice. These findings, with other data, support a division of labor in medial amygdala according to the reproductive or defense-related potential of the stimuli. There is some evidence for a convergence of information on conspecific and heterospecific threatening stimuli but, so far, the details are not entirely consistent. In our experiments with hamsters and mice, stimuli from potential predators (cat urine, cat collar) like other heterospecific stimuli, activated MeA and not MeP. Others studying mice found activation in ventral MeA (MeAv) during male-male interactions and in MePv by cat collar stimuli. *Since the submission of this paper we have also found activation in mouse MePv by stronger cat collar stimuli (see note at end of text).*

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1. Introduction

For chemosensory signals used for social and reproductive communication within a species, often called pheromones, the meaning of the signal generally does not have

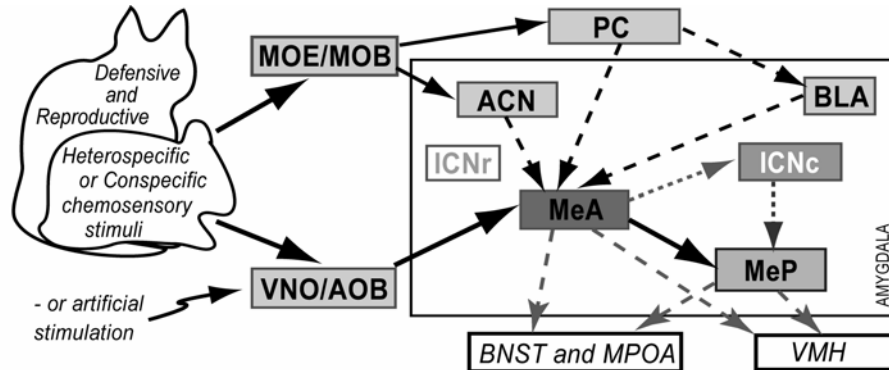


Fig. 1. Simplified diagram of chemosensory circuit in amygdala. Vomeronasal input via accessory olfactory bulb (VNO/ AOB) is analyzed in anterior and posterior medial amygdala (MeA, MeP). MeP appears to be inhibited by intercalated nucleus (ICNc) for heterospecific and artificial stimuli. MOE/ MOB: Main olfactory epithelium/Main olfactory bulb. ACN: Anterior Cortical Nucleus. PC: Piriform Cortex. BLA: Basolateral amygdala. ICNr: rostral part of medial intercalated nucleus. ICNc: caudal part of ICN. MPOA: Medial Preoptic Area. VMH: Ventro-medial hypothalamus.

to be learned. Appropriate physiological and behavioral responses elicited from recipients of same species (conspecific) are unlearned, unconditioned, and pre-programmed. In mammals, the vomeronasal organ is a primary detector for these signals. Its high sensitivity and selectivity are well adapted for recognition of particular molecules or combinations with pre-programmed meanings. The main olfactory system is generally of primary importance for learning complex odor signatures of individuals, places, foods, etc., so they may be recognized later, without the individual components or even particular combinations having any *intrinsic* meaning. However, in some species, the main olfactory system may also be a primary detector for some pheromones (Keller, Douhard, Baum, Bakker 2006) but it is not yet clear whether it is essential for this information to be routed to the amygdala, as it is for vomeronasal input. There are also special cases where the vomeronasal system may be a primary detector for learned chemosensory signals, as in the Bruce effect (Brennan, Kaba and Keverne 1990). Many species also rely on chemosensory systems for information about potential predators, prey and competitors, taking advantage of their ability to detect signals used for intraspecific communications of the other (heterospecific) species. The main olfactory system could discriminate any of these signals, once learned, but a surprising number of the signals used for intraspecific communication also activate the accessory olfactory bulbs and the vomeronasal systems of other species, without prior exposure or learning (Meredith and Westberry 2004). Thus, both olfactory and vomeronasal systems can potentially carry information important for (unlearned) recognition of conspecific mating partners or competitors and heterospecific competitors, predators or prey. These signals are distinguished and identified by central chemosensory circuits, especially the medial amygdala, the principal target of vomeronasal input. The medial amygdala is also the site of convergence of vomeronasal and olfactory

input and the source of onward projections to basal forebrain areas important for reproductive, defensive and other critical behaviors (Meredith 1998). Thus, it forms the nexus between sensory input and central executive functions, where unconditioned sensory signals can be interpreted and decisions about their relevance for different behaviors may be made. The amygdala is also important for assigning affective/ motivational value to sensory signals of all types. Thus, it is an interface where unconditioned stimuli with pre-programmed meaning and value, and conditioned signals with variable meaning and value, converge. Here we report on ongoing experiments to define the medial amygdala contribution to analysis of unconditioned stimuli.

2. Methods

General methods were similar to previous reports (see Meredith and Westberry 2004). Briefly, we exposed male hamsters and mice to cotton-tipped swabs containing chemosensory stimuli from males and females of the same or different species, for 15 min in a clean cage with clean bedding, renewing the swab at 3 min intervals. After a further 45 min, the animal was anesthetized and perfused for

HAMSTER (Meredith, Westberry, Blake)			MeAd	MeAv	MePd	MePv	ICNc
Hamster Vaginal Fluid	HVF	Repro./ Con-specific	++		+++		reduced
Female FI-Gland Secr.	fFGS	Repro./ Con-specific	++		++		0
Male FI-Gland Secr.	mFGS	Defense/ Con-sp.	++		+	+++	++
Female Mouse Urine	fMU	Neutral/ Hetero-sp.	++		0		++
Male Mouse Urine	mMU	Neutral/ Hetero- sp.	++		0		++
Male Cat Urine	mCU	Defense/ Hetero- sp.	++		0		++
Cat Collar (weak)	CC	Defense/ Hetero- sp.	++		0		NA
VNO Electrical stimulation	Artificial		++		0		++
AOB Drug stimulation	Artificial		++		0		NA
MOUSE (Meredith, Samuelsen)			MeAd	MeAv	MePd	MePv	ICNc
Hamster Vaginal Fluid	HVF	Neutral/ Hetero-sp.	++	++	0	0	+
Female FI-Gland Secr.	fFGS	Neutral/ Hetero-sp.		+		0	NA
Male FI-Gland Secr.	mFGS	Neutral/ Hetero-sp.		+		0	+
Female Mouse Urine	fMU	Repro./ Con-specific	++	++	++	++	NA
Male Mouse Urine	mMU	Defense/ Con-sp.	++	++	0	+	0
Cat Collar (weak)	CC	Defense/ Hetero-sp.	0	++	0	0	NA
MOUSE (Choi et al. 2005)			MeAd	MeAv	MePd	MePv	ICNc
Female Mouse Urine	fMU	Repro./ Con-specific		NA	*Lhx6 ++	+	NA
Male Mouse Urine	mMU	Defense/ Con-sp.	NA	**Lhx5 ++	0	NA	NA
Cat Collar (strong)	CC	Defense/ Hetero-sp.		NA	0	** ++	NA

* projects to VMHvl ** projects to VMHdm

immuno-cyto-chemical analysis of brain sections for immediate-early gene (IEG) protein and/or cellular markers of cell phenotype. An increase in the protein products of the IEG, *c-fos* (FOS) and of *Fos-related* genes (Fos related antigens or FRAs) occurs when neurons are activated. FRAs expression is activated in some neurons that do not show significant increases in Fos expression, as in the GABA-ergic intercalated nucleus cells described here. Stimuli used here included the following

(see also Table 1): (1) Conspecific for hamsters: female Hamster Vaginal Fluid (HVF; diluted 1:10), female and male Flank Gland Secretion (fFGS, mFGS; wiped from the gland). (2) Conspecific for mice: female and male urine (fMU, mMU; 1:10). (3) Heterospecific for both: male Cat Urine (mCU; 1:10), pieces of cat collar (CC). (4) Clean Swab control (CS). These stimuli included potential reproductive signals for males (female stimuli), indicators of conspecific competitive threat (male stimuli) and indicators of heterospecific predatory threat (cat stimuli). Mouse stimuli are heterospecific for hamsters and vice versa, and both may indicate potential competitors for resources. In other experiments referred to here, we explored the source of sensory information about these stimuli by removing vomeronasal organs from sexually naïve or experienced male hamsters, by ablating olfactory sensory neurons with intranasal infusion of ZnSO₄ solution, or by artificially stimulating sensory pathways, using methods described previously (see below).

3. Vomeronasal Input Analyzed Centrally by MeA/MeP Circuit

In male hamsters, we find that investigation of conspecific and heterospecific chemosensory stimuli elicits categorically different responses in medial amygdala of sexually-naïve intact animals. The primary sensory input to the anterior and posterior medial amygdala (MeA and MeP) is from the vomeronasal organ (VNO) via the accessory olfactory bulb (AOB) (Meredith 1998). MeA and MeP are strongly and reciprocally connected, but there is a denser afferent sensory projection to MeA from the AOB, suggesting a predominant flow of sensory information from AOB to MeA to MeP (Fig. 1). Removal of vomeronasal organs (VNX) in sexually inexperienced (naïve) male hamsters severely impairs mating behavior as well as activation of medial amygdala by reproductive chemosignals (Fewell and Meredith 2002). Activation of medial amygdala by other conspecific and by heterospecific chemosignals is also lost after VNX, suggesting that behaviorally important signals do not have the ability to activate medial amygdala via the main olfactory system in naïve male hamsters (Westberry and Meredith unpublished data). Elimination of main olfactory input by intranasal infusion of ZnSO₄ does not affect mating or activation of medial amygdala in hamsters (Meredith and Westberry 2004). Thus, vomeronasal input is necessary for normal mating in naïve males and olfactory input is not sufficient, suggesting that high sensitivity and selectivity of vomeronasal sensory neurons (Leinders-Zufall, Lane, Puche, Ma, Novotney, Shipley and Zufall 2000) may provide a pre-programmed signal identifying appropriate mating partners. Some regions of amygdala are activated during reproductive and agonistic behavior (Kollack-Walker and Newman 1995) and could be a route for pre-programmed recognition of conspecific competitors as well as mates.

4. Conspecific Signals are Analyzed in MeP in Hamsters and Mice

In male hamsters, we presented conspecific chemosignals from female or male hamsters on cotton swabs (Meredith and Westberry 2004) and found they activate

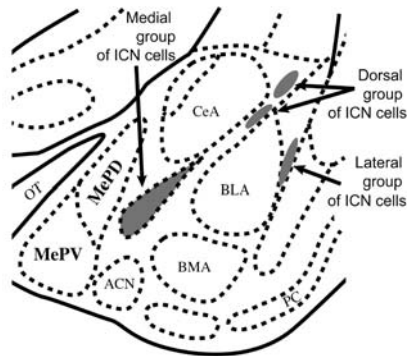


Fig. 2. Relative location of medial, basolateral and intercalated nuclei in the amygdala. Modified from drawings in the Morin and Wood (2001) atlas.

immediate early gene expression (Fos or FRAs) in both anterior medial amygdala (MeA) and posterior medial amygdala (MeP). Chemosignals used for the same kinds of communication but by other (heterospecific) species, e.g. male or female mouse urine or cat urine, all activated MeA and suppressed MeP in male hamsters (see Fig. 1 in Meredith and Westberry 2004; Table 1). With hetero-specific stimulation, the caudal part of the medial intercalated nucleus (ICNc), a group of GABA-immunoreactive (ir) cells (Meredith and Westberry 2004) adjacent to MeP (Fig. 2), was also activated and could be responsible for suppression of MeP. Artificial stimulation of the VNO sensory pathway by electrical stimulation in VNO or by drug-stimulation in AOB (Nolte and Meredith 2005), also activates MeA but not MeP. VNO stimulation, also activates ICNc (Meredith and Westberry 2004). Either type of artificial stimulation would produce a general, synchronous activation of input neurons (to AOB or to MeA/MeP) without regard to their normal response to any chemosensory stimulus (non-sense signals). We concluded (Meredith and Westberry 2004) that the amygdala circuit categorizes natural communication stimuli as socially-relevant (conspecific) regardless of their particular social function, or as not socially relevant (heterospecific and artificial). This categorization is not seen in the responses at the AOB level in hamsters (Meredith and Westberry 2004). Responses in the AOB of mice (Luo, Fee and Katz 2003) clearly discriminate between multiple criteria within the range of strain and gender stimuli present in mouse chemosensory signatures. It is not clear whether this is a higher order analysis (categorization) or simply a response to different combinations of chemicals in the different stimulus sources.

All socially relevant information appears to be routed to MeP but different conspecific social signals clearly activate different groups of neurons in MeP, which are distinguished to some extent by location within MeP and by cell phenotype. Thus, MeP could be important for deciding appropriate social response. For example, within MeP two conspecific reproduction-related stimuli (HVF, fFGS) strongly activate cells predominantly in the dorsal portion (MePd) and predominantly cells that are GABA-Receptor (GABA-R)-ir (Table 1). HVF activates few GABA-ir cells but fFGS activates more (Westberry and Meredith, unpublished data). Responses to these signals in MeP contrast with responses to male flank-gland secretion (mFGS), which activates predominantly GABA-ir cells in MeP, predominantly in MePv. Male hamsters flank mark competitively to signal their

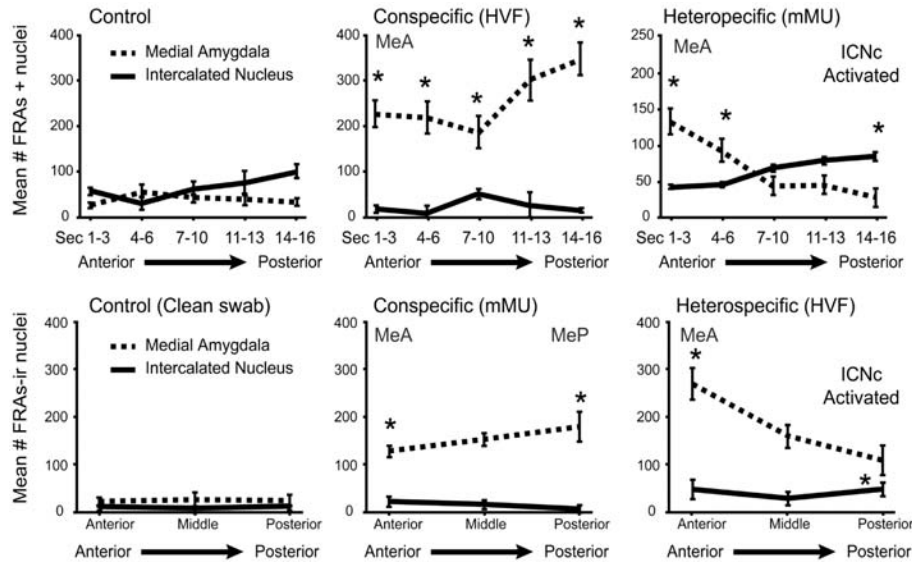


Fig. 3. FRAs expression within medial amygdala and ICN averaged over sets of three serial sections from MeA to MeP - for hamster (top) and mouse (below). The same two stimuli were used, each conspecific for one species, where it activates MeA and MeP, and heterospecific for the other, where it activates MeA and ICN. Control values for hamster were taken from animals perfused 15 min after exposure to HVF, before significant FRAs expression begins. * $p < 0.05$ compared to control at that site (ANOVA).

presence to females (Cohen and Johnston 2001), so mFGS from other males signals a competitive threat and belongs in a conspecific threat-related or defense-related sub-category. All three of these conspecific stimuli activate MeP (in addition to cells in MeAd and MeAv, Table 1), but the defense-related and reproductive stimuli activate different cells and in different but overlapping subareas of MeP. All stimuli we used were unfamiliar to the test animals so these responses relate to categories of animals not to individuals.

We reasoned that hamster and mouse chemosignals should activate medial amygdala in those two species in reciprocal ways. In our preliminary experiments with mice, we find that they do. In mice, conspecific (mouse) stimuli activate MeA and MeP but heterospecific (hamster) stimuli activate only MeA. Female mouse urine (fMU), a conspecific-female reproductive stimulus, activates MeA (both dorsal and ventral) and strongly activates posterior dorsal Me (MePd) in male mice. The equivalent hamster reproductive stimulus, HVF, activates MeA but not MeP in mice; as fMU does in hamster. The conspecific-male defense- or threat- related stimulus for mice, equivalent to mFGS for hamsters, is male mouse urine (mMU). We find significant activation of MePv by this defense-related conspecific-male stimulus, as well as significant activation in MeAd and MeAv (see Table 1). We do not yet know whether these cells have the same transmitter phenotype as those activated by mFGS in male hamsters. We do have preliminary evidence that heterospecific stimuli activate ICN in mice as in hamsters. Figure 3 shows activation of IEGs (FRAs) in medial amygdala and ICN in serial sections through the anterior-posterior extent of

medial amygdala (MeA and MeP) in hamsters and mice. The results in mice are preliminary, involving few animals, but are clearly similar to those in hamster. The same two stimuli (HVF, mMU) were used, each conspecific for one species and heterospecific for the other. In both cases, anterior sections showed activation with both stimuli in MeA and posterior sections showed activation in MeP only for the stimulus that was conspecific (HVF for hamsters, mMU for mice). In the same sections, posterior sections showed activation of caudal ICN (ICNc) only for the heterospecific stimulus (mMU for hamsters, HVF for mice).

5. MeA/MeP is Essential for Evaluation of Conspecific Signals

The accessory olfactory bulb (AOB), supplies neural input to medial amygdala circuits from two distinct sets of vomeronasal sensory neurons (VSNs) but shows no evidence of the categorization of responses seen in MeA/MeP (Meredith and Westberry 2004). The amygdala response appears to be a second stage analysis of the chemosensory information and a place for integration with olfactory input. We suggest MeA, MeP and ICN constitute a preprogrammed neural circuit that selects signals for further (tertiary) analysis by more central circuits, and directs reproductive signals for analysis by the steroid-receptor rich circuits of MeP and Bed Nucleus of Stria Terminalis (BNST) (Wood, Brabec, Swann and Newmann 1992). Lesions of MeA that spare the medially located (superficial) AOB input to MeP eliminate mating behavior in male hamsters, whereas lesions of MeP alone disrupt, but do not eliminate, mating in laboratory tests (Lehman and Winans 1982). However, the greater deficit after MeA lesions may result in part from the disconnection of MeA input to MeP. So, both areas may actually contribute more equally to mating behavior. Microinjections of steroid hormones in MeP are sufficient to restore mating behavior in castrated male hamsters, but only if the area supplied with hormone also has intact chemosensory input (Wood and Coolen 1997). Lesions of medial amygdala also affect defensive behavior (Luiten, Koolhaas, deBoer and Koopmans 1985), which is also modulated by steroid levels. Thus, control of chemosensory input to MeP, which appears to be one function of the categorical circuit, may ensure that species-typical social behavior in naïve animals is limited to appropriate situations signalled by conspecific stimuli.

6. Reproductive and Defensive Functions of Medial Amygdala

The differential activation of subareas of MeP by reproductive and conspecific threat/defensive stimuli in hamster is generally consistent with the proposals of Canteras and colleagues (Canteras 2002, Petrovich, Canteras and Swanson 2001). From tracing experiments in rats, they suggest that medial amygdala is divided into subareas concerned with reproductive and defensive stimuli, each connected to subareas of the hypothalamus with the same function. Following these proposals, Choi, Dong, Murphy, Valenzuela, Yancopoulos, Swanson and Anderson (2005) investigated responses in medial amygdala of male mice, in cells expressing different

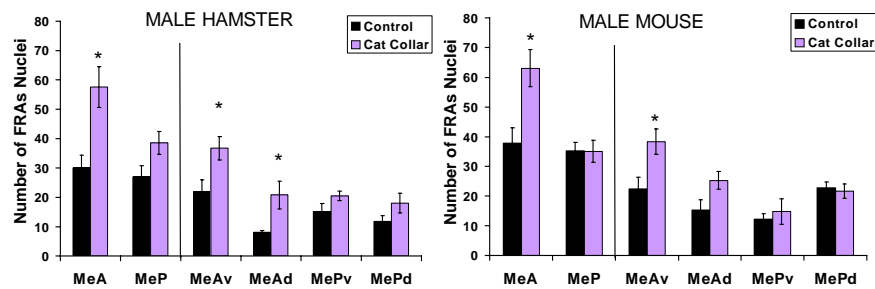


Fig. 4. One-cm pieces from a cat-collar worn by a male cat for 7-12 hrs activate MeAv and MeAd in hamster (left) and MeAv in mouse (right) but did not activate MeP (* Hamster, MeA $p < 0.001$; MeAv $p < 0.02$; MeAd $p < 0.04$; Mouse, MeA, MeAv $p < 0.01$ – all vs Control; ANOVA).

LIM-Homeo domain proteins. These proteins are critically involved in axon guidance in other areas of the brain. In a technically wide-ranging report, Choi et al. (2005) found strong IEG (*c-fos* or *Fos*) activity in *Lhx-6* positive cells in response to a conspecific reproductive stimulus (fMU). In agreement with our studies and those of others in mice, hamsters and rats (Baum and Everitt 1992), these activated cells are located in dorsal posterior medial amygdala (MePd). The majority of activated cells in this area were *Lhx-6*-positive. Some of these projected to the ventrolateral (reproductive) part of the Ventromedial Hypothalamus (VMHvl), as predicted by the Canteras hypothesis, but the proportion of activated cells that fell into this category is unclear. Unlike the cells activated in hamster by reproductive stimuli, these *Lhx-6* positive cells are glutamic acid decarboxylase (GAD)-positive and probably GABAergic. A discrete group of cells in ventral MeA express another LIM marker, *Lhx5-ir* and project to the dorsomedial part of the Ventromedial Hypothalamus (VMHdm), a component of the putative defensive circuit. These cells were apparently not examined after chemosensory stimulation alone, but were strongly activated during male-male agonistic encounters in mice. They express *vGlut2*, a glutamate transmitter transporter, and do not express GAD. So, they are not the displaced equivalents of the cells activated in MePv in hamsters. We have recently acquired the antibody to *Lhx5* (courtesy of Dr. Tom Jessel) and also find a patch of cells positive for *Lhx5* in hamster MeAv. We do not yet know whether these *Lhx5* cells in hamster respond selectively to mFGS, the conspecific-male defence-related stimulus for hamsters. They are located within the extensive region of MeA activated by mFGS, but this region also responds to most other natural stimuli tested. *Lhx5*+ cells are widespread in the hamster brain, so it is not a unique marker for cells responsive to conspecific-male stimuli or VMHdm projecting cells.

Table 1 includes data from Choi et al. (2005) for comparison with our studies on activation of medial amygdala and subareas in hamsters and mice. They concentrated on whether cells with an identified phenotype respond to particular stimuli and project to the hypothalamic subnuclei predicted by the Canteras hypothesis, but did not systematically report on other cells or other areas.

In Choi et al.'s (2005) experiments, a group of cells located in MePv and projecting to (defensive) VMHdm, but not labeled with a LIM phenotype, was activated by predator stimuli (pieces of collar worn by a cat - CC). Activation of

cells in this area by cat odor is also well established in rats (McGregor, Hargreaves, Apfelbach and Hunt 2004). We did not see activation in this area of hamsters by male cat urine (mCU) (Meredith and Westberry 2004) but this may not be the most potent predator related stimulus from cats (McGregor et al. 2004). We tested pieces of cat collar as stimuli for both hamsters and mice but found only the standard heterospecific pattern of amygdala response, with activation of MeA but not MeP. A separate statistical analysis of dorsal and ventral subdivisions of MeA and MeP did not find any activation even in MePv (Fig. 4). However, our cat collars were worn by the cat for only 7-12 hrs compared with 2 weeks for collars used by Choi et al. and in other previous experiments. We believe the shorter time should be sufficient to acquire a distinguishable odor but there is evidence for an intensity-related factor in the behavioral response to cat odor stimuli by rats (Takahashi, Nakashima, Hong and Watanabe 2005) and our stimulus may have been too weak.

Summary: There is agreement across studies in designating response in dorsal posterior medial amygdala (MePd) as likely to be reproduction-related, but there appears to be a mismatch between the transmitter phenotypes of the cells predominantly activated in hamsters (non-GABA-ir) and reported in mice (GAD-positive). Ventral medial amygdala (MeAv, MePv) may be an area where both conspecific and heterospecific defence-related stimuli are represented. These stimuli are not equivalent, but some of the behavior they elicit is similar. MePv is activated by conspecific threat-related stimuli, mFGS in hamsters and mMU in mice, and by heterospecific threat stimuli (cat collar, CC) in mice. The cells in MePv that predominate in responses to conspecific threat in hamsters (GABA-ir) and in responses to heterospecific threat in mice (non-GAD-ir) could be two co-existing populations. Resolution of this question will require further work. Choi et al. (2005) did not report on activation in MePv by conspecific male stimuli and our failure to see activation there with cat stimuli may be related to intensity of stimulation. The strong activation of Lhx5 cells in MeAv during male-male agonistic interactions reported by Choi et al. (2005) in mice is not clearly matched in our experiments by a selective activation of this area by conspecific-male defence-related stimuli (mFGS) in hamsters or by mMU in mice. In future experiments we will use a wider range of stimuli and more extensive tests to evaluate cell phenotypes; and we will complement IEG methods with electrophysiology in order to resolve these conflicts. This will provide a more complete account of medial amygdala function in discriminating between stimuli and, perhaps, in deciding on an appropriate response.

Note added in proof: In work completed after the submission of the manuscript we find that cat collar stimuli do activate ventral posterior medial amygdala (MePv) in mice, as reported by Choi et al 2005, if the collars were worn by the cat for 2 weeks. We have also confirmed that collars worn for 12 hrs do not activate MePv (Samuelson, C. and Meredith, M., unpublished data).

Acknowledgements

Supported by NIDCD grant DC 5813 from the U.S. National Institutes of Health.

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11 Selective Response of Medial Amygdala Subregions to Chemosignals

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