Published in final edited form as:

Brain Res. 2019 April 15; 1709: 33–38. doi:10.1016/j.brainres.2018.03.021.

Noradrenergic effects on olfactory perception and learning

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Abstract

We here review modulation of olfactory guided behavioral tasks by noradrenaline. In this review we focus on modulation of the main olfactory system in adult rodents. We detail behavioral paradigms commonly used and discuss how sensory perception and learning can be measured using these paradigms. We then describe neuromodulatory effects on several aspects of olfactory processing, including detection and encoding. We describe how memory duration, specificity and duration are affected by noradrenergic modulation.

Keywords

Noradrenaline; olfaction; signal to noise ratio; neuromodulation; behavior

1. Introduction

Norepinephrine (NE) plays important roles in the detection, learning and memorization of olfactory sensory stimuli (Linster et al., 2011). As in other systems, NE has been implicated in signal to noise ratio (S/N) modulation of olfactory stimuli, plasticity associated with olfactory learning and the ability to discriminate odorants. We here review its role in adult rodent olfactory processing with emphasis on olfactory behavioral studies. NE's role in neonatal olfactory learning has been described in detail elsewhere and seems unrelated to adult processes due to substantial changes in the olfactory and noradrenergic system after a critical period (Moriceau et al., 2009a, Moriceau et al., 2009b). The modulation of olfactory guided behaviors in adult rodents is complex and variable, ranging from effects on detection thresholds to effects on memory duration, mediated by common underlying neural and synaptic mechanisms.

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2. Olfactory guided behaviors

Olfaction is an important sense for most animals, implicated and necessary for multiple processes such as acquiring food, recognizing mates and conspecifics and identifying potential dangers. These processes involve detection of an odorant, often at low concentrations and masked by background odorants, identifying this odorant, and possibly memorizing it (Cleland, 2011). Some of these processes are non-associative, e.g. recognition of a previously encountered odor, some are associative, e.g. associating an odor with a predicted outcome (food, predator, shelter). In laboratory settings, a number of paradigms allow to measure the efficacy and features of odor processing (Figure 1). In combination, these allow to assess odor detection and identification, odor recognition, as well as encoding, strength, specificity and duration of an odor memory. It is important to note the encoding, duration and specificity of odor memories are not independent of each other but rather are interdependent (Freedman et al., 2013, Hackett et al., 2015). Briefly, among non- reward driven behaviors, odor recognition and habituation paradigms are common. In an odor recognition paradigm, an animal is allowed to investigate an odor for a short period of time during an encoding trial (Figure 1Ai). After a delay, the animal is presented with the encoded odor and a novel odor during a recall trial. The animal is considered to remember the encoded odor if it investigates the novel odor significantly more (Figure 1Aii). This paradigm allows to test memory specificity by varying the similarity between the encoded and novel odor (Figure 1Aiii), as well as memory duration by varying the delay time (Figure 1Aiv). A habituation paradigm is similar but allows for multiple encoding trials followed by multiple recall trials, hence memory formation can be observed in addition to other parameters (Figure 1Bi). In reward associated paradigms, an odor is paired with a reward, the animal learns this association and expresses the association by responding to the odor (Figure 1Ci and Di*****). An odor can be paired against another odor to create a discrimination task (Figure Di). We find that when testing odor detection or discrimination capabilities in rats and mice, results differ between non-reward driven or reward driven paradigms. For example, while the enantiomers of limonene are not discriminated in an odor recognition or habituation task, rats can learn to discriminate them after just a few reward driven trials (Linster et al. 2002). Rats are able to detect odorants at much lower concentrations when motivated by reward than in spontaneous detection tasks (Escamilla et al 2012). Feedback to the olfactory bulb is necessary to successfully learn a reward-guided but not a spontaneous odor task (Kiselycznyk et al. 2006), suggesting a strong role for central projections to the olfactory bulb for reward guided odor tasks.

Any of these paradigms can be employed to assess the role of a neuromodulator for odor processing by manipulating the presence and/or efficacy of this modulator either locally or globally, short term or long term, via a number of experimental methods (Figure 2A).

3. NE modulation of olfactory processing

Odor detection

Odor detection is the first step in odor processing. The olfactory system is built to facilitate odor detection with a very high ratio of sensory to principal neuron projections facilitating the detection of even very low concentration odors (Cleland and Linster, 2005). Odor

detection abilities could potentially be modulated by NE via increased excitability of principal cells (Linster et al., 2011), increased overall inhibitory tone leading to a decrease in baseline spontaneous activity (Nai et al., 2009, Nai et al., 2010) as well as changes in dynamics and synchronization (Linster et al., 2011). A first experiment in rats testing detection thresholds after chemical ablation of NE fibers in the olfactory bulb (OB) showed no effect of this depletion on odor detection thresholds (Doty et al., 1988). Later experiments showed a significant effect of local additions of NE into the OB on odor detection thresholds, lowering these from 10^{-2} Pa vapor partial pressure to 10^{-4} vapor partial pressure at the highest dosages of NE infused (Escanilla et al., 2010) (Figure 3A). Importantly, these experiments used a spontaneous, non-associative paradigm (Figure 1B) in which rats are not motivated by outside factors to detect the odorants. Blockade of NE to the OB in a reward driven detection task similar to that employed by Doty et al (1988) lowered rats' abilities to detect very low concentration odorants (Escanilla et al., 2012) (Figure 3B). Because spontaneous and reward-driven tasks often yield differential results, as detailed above, one might expect differential effects of NE function on this tasks as well. A pioneer study by Gray et al (1989) showed that odor driven dynamic properties of the olfactory bulb could be modulated by NE only when the odor was associated with a shock, suggesting a differential role for NE in spontaneous versus motivation driven odor processing.

Odor memory encoding

Encoding is a process by which a sensory stimulus is represented by neural activity signals and can be used for future retrieval or comparison to other odorants. While it is difficult to assess encoding after a single representation, when using paradigms with multiple encoding trials the speed of encoding can be assessed by comparing responses on successive trials. When using the habituation task (Figure 1B) encoding can be monitored by observing investigation times over successive trials. A chemical depletion of LC neurons led to a severe deficit in acquisition in mice, which was counteracted by local bulbar NE infusions (Guerin et al., 2008) (Figure 4Ai). In contrast, blockade of OB alpha and beta NE receptors did not lead to a change in odor encoding in rats using the same paradigm (Mandairon et al., 2008a) (Figure 4Aii). In reward associative tasks, the encoding process, monitored by speed of acquisition, was impaired in several different paradigms in rats and in mice only if alpha and beta bulbar NE receptors were blocked (Doucette et al., 2007, Mandairon et al., 2008a) (Figure 4Bi) and perceptually very similar odors were used. As a consequence, acquisition speed in two odor discrimination tasks reflect encoding of the odors as well as discrimination of these odors; use of a single task can often not differentiate between these two processes. Activation of the NE system through electrical stimulation led to encoding of an odor (Shea et al., 2008) without a behavioral correlate, evidenced as a lack of interest in that odor after a 24 hour delay. Overall these experiments show evidence for a role for NE in olfactory odor encoding with detailed mechanisms still left to be investigated (de Almeida et al., 2015).

Odor memory specificity

Each encoded memory, depending on behavioral state and circumstances, will be more or less specific to the stimulus encountered at the time of encoding. This specificity is expressed as generalization gradients (Cleland, 2012) or a lack of discrimination between

the encoded and an overlapping stimulus. In olfactory paradigms, the specificity of a formed memory can be assessed in an odor recognition paradigm (Figure 1A), habituation paradigm (Figure 1B), odor-reward association paradigm (Figure 1C) as well as in go/no-go type discrimination paradigms (Figure 1D). In each case, responses to the encoded odor are compared to novel, non encoded odorants of varying similarity. Several groups have shown that NE regulates odor similarity as expressed by the specificity of the encoded memory, in non-associative as well as associative paradigms (Doucette et al., 2007, Mandairon et al., 2008b, Escanilla et al., 2010). This effect may be related to the modulation of inhibitory processes in the OB and piriform cortex (PC) which changes the overlap in neural representations between odorants.

Odor memory duration

The duration of an odor memory can be tested using all the paradigms mentioned above. With respect to NE modulation, studies using the olfactory recognition paradigm have shown that NE modulates the duration of olfactory memory. Veyrac et al. showed that in mice, depletion of NE in the brain decreased memory for an encoded odor to less than 15 minutes, whereas enhancement of NE in the brain increased memory duration to 30 minutes (Veyrac et al., 2007). In contrast, Manella et al. showed that local OB NE infusions can modulate odor recognition memory duration in a dose dependent manner, with low and high dosages of NE decreasing memory duration and medium dosages having no effect (Manella et al., 2013) (Figure 4C). Because these manipulations are local, direct and highly dose-dependent, and manipulations of other groups include global depletion or global enhancements of NE, these results are difficult to directly compare and the apparent contradictions may result merely from procedural differences.

Perceptual learning

Perceptual learning falls into a somewhat separate category for odor learning in that animals learn in the absence of a behavioral paradigm merely via exposure to odorants. The outcome of this learning is most often tested via a habituation or odor recognition paradigm, as depicted in Figures 1Ai and Bi. Perceptual learning changes both odor discrimination capabilities supposedly by modulating bulbar odor representations (Mandairon et al., 2006a, b) as well as recognition memory duration (Figure 1Ai; Rochefort and Lledo, 2005). Perceptual learning depends on the integration of adult born neurons in the OB (Moreno et al., 2009) and expresses for about 4 weeks after the initial learning event. Interestingly, perceptual learning also depends on NE modulation in the OB (Moreno et al., 2012), although the exact mechanisms of this dependence are not yet known.

4. Experimental considerations

As reviewed in Figure 1, labs employ a variety of behavioral paradigms to assess the role of NE modulation for olfactory processing. Because task parameters such as odor concentration, choice of odorants, intertrial intervals, to just name a few have a significant effect on task outcomes (Cleland et al., 2009, Freedman et al., 2013, Hackett et al., 2015) it can be difficult to directly compare results from different studies. Similarly, there are numerous ways to influence NE modulation during a task (Figure 2), all of which affect the

system in different ways. Because the effects of NE are non-linear and non-monotonic due to different receptor affinities (reviewed in (Linster et al., 2011)), the dosage of NE has a large effect on the modulatory effects. Global manipulations like chemical depletion of NE neurons, electrical stimulation of NE neurons or global drug injections will have very different effects from local manipulations such as local infusion of NE or antagonists. These experimental factors are important to consider when comparing seemingly contradictory behavioral outcomes. These can only be resolved by collecting more cellular and synaptic data in conjunction with behavioral experiments and computational modeling. Computational model can test a range of possible scenarios for modulating NE and compare these to behavioral observations. Task differences present a challenge but also provide information to narrow down mechanisms.

5. Conclusion

The behavioral studies reviewed in this paper show that NE modulation can effect all aspects of olfactory processing: detection, encoding, retrieval, specificity and duration of an encoded odor memory. Typically, non-reward associative tasks are more strongly affected by manipulations of the NE system than reward motivated tasks, a phenomenon we are currently investigating in more detail. To better understand these data, one has to correlate these results with cellular, synaptic and network data gathered. This necessitates theories as to what parameters of neural coding determine events like encoding or retrieval of an odor and how these are interconnected. For example, one could propose that increased oscillatory dynamics in the OB leads to higher spike synchrony, which in turn leads to higher S/N, better odor detection, faster learning and as a consequence longer memory duration. In the end, only specific differentiation of effects will allow to determine the effects specifically. For example, we have shown in a recent study that NE, but not ACh modulates odor detection thresholds, while both modulate memory specificity (Escanilla et al., 2012). These types of differentiation then allow to search for mechanisms modulated by one but not the other substance. In summary, behavioral data has to be accompanied by electrophysiological and computational studies to elucidate the overall effects of behavioral states on sensory processing. In general, modulatory effects of NE can only be understood when embedded in a coherent understanding of the neural mechanisms studied. NE inputs will usually change and modulate ongoing processes, which means that without a coherent understanding of what these processes are we cannot proceed. A single behavioral paradigm, as well as a single method of NE manipulation, will provide limited, possibly misleading answers. One advantage of a computational approach is that it allows integration of many different results into a single framework. We can build models for a number of computations the system has to perform, for example detection, discrimination and associative learning. Each can be tested separately in behavioral paradigms. A computational approach would need to be compatible with all three types of experiments and be able to correlate neural data with each of these. As a consequence, computational approaches allow to build models with multiple functionalities and test how these coordinate and interact.

Acknowledgments

Funding: Original research reviewed in this article was funded by NIH/NIDCD grant DC008702.

Abbreviations

NE	Noradrenaline
OB	Olfactory bulb
LC	Locus coeruleus
S/N	Signal to noise ratio

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Noradrenergic modulation of olfactory guided behaviors is reviewed

Non-linear effects of modulation are discussed

Effect types are compared across experimental approaches

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Figure 1.

Behavioral paradigms used to test olfactory detection, encoding, recall and memory. **A.** Odor recognition. **A_i**. In this paradigm, animals are first presented with an odorant during an encoding trial. After a delay (5–50 minutes in rats), animals are presented with the encoded odor and a second, novel odor and investigation in response to each odor is recorded. **A_{ii}**. Typically in this paradigm rats investigate the encoded odor significantly less than the novel odor, which is interpreted as memory for the encoded odor. **A_{iii}**. This paradigm allows to test the specificity of the formed memory by presenting novel odors with increased chemical or perceptual similarity to the encoded odor. Specificity is measured as the ratio in response to the novel versus the encoded odor. **A_{iv}**. The duration of the encoded memory is measured by increasing the intertrial delay and comparing investigation of the encoded odor during the trials. **B.** Habituation paradigm. **B_i**. In this paradigm the animal is presented with a same stimulus during repeated trials separated by relatively short intervals (typically 5 minutes in rats). After encoding or habituation, the animal is presented with the encoded odor and/or test odors during the last trials. **B_{ii}**. This paradigm allows to study encoding, measured as the slope of decrease in investigation over successive trials, specificity indicated by cross-habituation to novel odorants, and duration, measured as the time over which the response to the encoded odor recovers. **C.** Reward association paradigm. **C_i**. In this paradigm the animal learns to associate a reward with an odorant over successive trials (typically 10–20 in rats). After this training, the animal is presented with the encoded odor or novel odors in extinction trials without reward. **C_{ii}**. This paradigm allows to measure the strength of encoding (time spend looking for the reward in response to the encoded odor), the specificity of the encoded memory (relative time spend looking for reward in novel, similar odors), as well as the duration (time spend looking for the reward in encoded odor after longer time intervals). **D.** Go/no go or odor discrimination task. **D_i**. In this task animals are presented with two odorants, one rewarded one not rewarded, either at the same time or sequentially. Animals learn to associate the odor with reward. **D_{ii}**. In this paradigm encoding is measured as the number of correct choices over the course of training, duration can be assessed by

retesting after an interval and specificity can be assessed by using novel, related odorants during testing.

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Figure 2.

Commonly employed methods to modulate NE processing during olfactory behaviors. The figure shows local (to a given circuit only) and global types of manipulations.

Figure 3.

NE modulation of odor detection. A. Odor detection thresholds were assessed using a habituation task. Rats were first habituated the carrier (mineral oil) during 5 trials and then presented with an odor ranging from 10⁻¹ to 10⁻⁶ Pa. Significant investigation of the odor was used to determine detection thresholds, with rats infused bilaterally into the OB with saline or NE (from Escanilla et al 2010). The graph shows detection thresholds as a function of NE concentration. B. Odor detection thresholds were assessed using a simultaneous go/no go task. Rats were presented with an unscented dish and a rewarded scented dish for 10 trials. The graph shows the percent correct choices made as a function of odor vapor partial pressure and experimental group. Note that rats with alpha and beta blocked locally in the OBs performed significantly worse in detecting odors at 10⁻³ and 10⁻⁴ Pa (from Escanilla et al 2012).

Figure 4.

NE modulation of odor encoding (A) and odor memory duration (B). A. Effect of NE modulation on non-associative odor encoding. Mice (Ai) or rats (Aii) were presented with an odorant over 4 (6) successive trials with five minute intertrial intervals. Odor encoding is defined as a significant increase in investigation of the odor over the course of the trials. Ai. Mice were treated with DSP4 to deplete NE neurons in the locus coeruleus and later infused with saline or NE bilaterally into the OBs. The graph shows that DSP4 treated mice infused with saline do not form an odor memory over the course of four trials and that local bulbar NE infusions rescue this deficit (Guerin et al, 2008). Aii. Rats were bilaterally infused with saline or NE receptor blockers. The graph shows that all groups formed an odor memory over the course of 6 habituation trials (Mandairon et al. 2008). Bi. Rats were bilaterally infused into the OBs with NE receptor antagonists before being trained on a simultaneous go/no go task. The graph shows the % correct choices made in 5 trial blocks. Rats with alpha and beta NE receptors blocked were impaired on the first 5 trials, evidencing a slowing down of the acquisition process. C. Rats were tested in the odor recognition paradigm with a 30 minute delay between the encoding and retrieval trials. The graph shows relative investigation times of the novel odor as a function of experimental group (local infusions of NE). Saline control rats and rats infused with a medium dose of NE expressed memory for the odor after 30 minutes, whereas rats infused with low and higher doses of NE did not (Manella et al. 2013).