where it is largely nuclear. A similar observation has been made for NEDD8 (Y. Chen and R. Neve, unpublished), which shows a pronounced change in intraneuronal localization in affected regions of AD brain. These findings might be related to the recent discovery [12] that phosphorylated histone H3, which is normally located in the nucleus, shows aberrant cytoplasmic localization in hippocampal neurons in AD.

Sumoylation as a potential therapeutic target

In summary, Li *et al*. [1] used a novel strategy to identify the existence of a new pathway that modulates α-secretase-mediated, rather than β-secretase-mediated, cleavage of APP (Fig. 1). This pathway presents a new set of targets for potential therapeutic intervention in AD. It has been difficult to generate β-secretase inhibitors; perhaps stimulation of sumoylation with SUMO-2, a natural inhibitor of β-secretase, will be a viable alternative.

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Wake up and smell the conspecific!

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Mammals regulate their behavior using odor cues called pheromones. These compounds are detected and recognized by neurons in the accessory olfactory system. New electrophysiological recordings in behaving mice by Luo, Fee and Katz reveal aspects of pheromone biology and how these stimuli are represented by single neurons.

For most mammals, reptiles and amphibians, the sense of smell consists of two distinct sensory systems. The better-studied main olfactory system detects volatile odorants, sampled by sniffing. By contrast, the accessory olfactory system (or vomeronasal system) detects stimuli often associated with pheromones – compounds that are used to signal between members of a species, typically for their mutual benefit [1]. These stimuli are pumped into the interior of the vomeronasal organ, with the resident sensory neurons sending their output to the accessory olfactory bulb (AOB) [2]. After the AOB, a relatively short series of projections leads to neuroendocrine areas in the hypothalamus [3]. The comparative brevity of this pathway might facilitate investigations of the neural basis for pheromone-driven behaviors.

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Luo and colleagues recorded the spiking activity of neurons in the AOB in awake, freely exploring mice [4]. To deliver pheromonal stimuli, they placed anesthetized mice of different sexes and strains in the test arena. Neural activity was compared with the behavior of the mouse as recorded on video. This experimental design permits only limited control of the stimulus parameters; in exchange, it insures the relevance of their findings to the natural function of this sensory system, a significant virtue in light of our incomplete knowledge of the nature of pheromonal stimuli. Indeed, some of the most intriguing aspects of their findings have to do with the nature of the stimuli themselves.

Robust sensory responses

Comparison with previous recordings in other olfactory systems highlights an important aspect of Luo *et al*.'s findings. In insects, robust odorant-coupled responses have been recorded in both the antennal lobe and the macroglomerular complex, the insect analogs of the main and accessory olfactory bulbs, respectively [5,6]. Similar responses have been found in recordings in the main bulb from anesthetized rodents [7]. However, in the main

olfactory bulb of awake rodents, the connection between neural activity and sensory experience has been more elusive. Previous investigators have documented significant variability in neural responses, obscuring the link between spiking responses and applied odorants [8–10]. In a study pairing odorants with a rewarded behavioral output, it was found that neural activity correlates more closely with the behavior of the animal than with the identity of the odorant [10]. This difference from anesthetized recordings might be due in part to the difficulty of finding a match between a large family of receptor types and a large repertoire of odorants. Alternatively, these differences could result from the extensive input to the main bulb from other areas [11], which might be more active in an awake preparation. In interpreting these previous recordings, it is notable that Luo *et al*. report, almost as an aside, robust odorant-coupled responses in 'control' recordings from the main olfactory bulb. It remains an open and important challenge to elucidate the various roles of odorants and other factors in the neural activity of the main olfactory bulb in awake rodents.

In the accessory olfactory system itself, scant precedent exists for Luo *et al*.'s findings. Because the vomeronasal organ receives its stimuli via a pumping mechanism activated during exploration [12,13], it is not straightforward to study the sensory responses of AOB neurons in an anesthetized preparation. In the apparently unique prior attempt [12], this problem was circumvented by stimulating the nasopalatine nerve, causing activation of the pumping mechanism, while blowing odorized air over the duct leading to the vomeronasal organ. This ingenious approach seemingly yielded small neural responses to the presented stimuli but it was apparently never pursued to the point of exploring the selectivity or sensitivity of AOB neurons.

Luo and colleagues obtained sizable neural responses when the test mouse investigated stimulus animals. It is possible that some aspect of the behavior of the mouse – for instance, the activity level of the vomeronasal pump – played a role in these responses. Because of their reproducibility, however, Luo *et al*.'s results [4] have the hallmarks of selective responses to pheromonal odorants.

Pheromones and neural circuits

These elegant studies have resolved a number of questions about the nature of pheromonal stimuli and their encoding by neurons of the AOB. First, neurons of the AOB responded only after direct contact, suggesting that vomeronasal neurons are not typically stimulated from a distance by volatile compounds in air [14,15] (but see Ref. [16]). Second, these neurons responded not only when the mouse was investigating the ano–genital regions, long known as a source of pheromones [17], but also when the mouse investigated the face. A small minority of their cells were indeed specific for the face, whereas none were specific for the ano–genital regions. Finally, neurons in the AOB were typically selective to particular combinations of sex and strain of the stimulus animals. This shows that significant differences exist in the identity or concentration of pheromones these animals emit, and that the AOB contains neurons sensitive to these differences. This finding provides a neural substrate for phenomena that require mice of different sexes and strains to be distinguished on the basis of their pheromonal odor. For example, in the pregnancy-block effect, a female mouse learns to recognize the scent of her mating partner and terminates her pregnancy if persistently exposed to a male from a different strain [18]. The neural changes required to encode this memory occur in the AOB itself [19].

The results of Luo *et al.* also provide insight into the function of the accessory olfactory system as a neural circuit. Responses began a few seconds after initial contact, but rose to their peak and fell over tens of seconds, similar to the duration of typical bouts of investigation. Although there are uncertainties in the time course of stimulus delivery to the vomeronasal organ, this finding is consistent with a fairly rapidly acting vomeronasal pump [13] and little or no desensitization of the receptor neurons during prolonged stimulation [20]. Neurons also display both excitatory and inhibitory responses, suggesting a process akin to the inhibitory interactions of the main olfactory bulb and antennal lobe [7].

Future directions

Recent studies have shown that certain pure compounds excite vomeronasal neurons [21,22] but Luo *et al.* were unable to find any responses to these compounds. Given the small fraction of receptor neurons that these compounds activate [21], it seems likely that sampling statistics are to blame. Alternatively, it is possible that carrier proteins are needed in the intact system to deliver stimuli to the vomeronasal organ [23–25]. Further studies with pure compounds could yield important insights into how AOB neurons represent chemical stimuli. Another important direction stems from previous studies showing that individual vomeronasal neurons are selective for sex, and in rare cases even for individuals, of the same strain [20]. It will be important to know whether the selectivity of neurons in the AOB differs from that of vomeronasal neurons, and if so, how the processing in the AOB contributes to this difference.

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Letter

Long-term memory: does it have a structural or chemical basis?

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A key characteristic of declarative memory is its permanency. The lifespan persistence of memory suggests that it has either a structural or chemical basis. Most current models of long-term memory suggest that traces of memory are stored by structural modifications of synaptic connections and that newly formed patterns of neural activity are carriers of memory traces. Newly learned memories pass through a labile stage before being consolidated into stable memories, and this transition can be disrupted by inhibitors of protein synthesis. This inhibition is regarded as evidence for the structural hypothesis in which protein synthesis is viewed as a required step in structural modifications of synaptic connections.

This paradigm has been challenged by observations that upon retrieval of well-consolidated memories, they pass through a labile state in which they are also vulnerable to protein synthesis inhibitors [1]. Interest for this phenomenon of memory reconsolidation has been stimulated by a recent experimental study by Nader and colleagues [2] followed by an elegant analysis in the February issue of *TINS* [3]. Nader *et al.* concluded that their finding was not predicted by the structural hypothesis because retrieval is unlikely to reverse the structural changes in synaptic connections induced by original learning [2].

The difficulty in explaining memory reconsolidation might reflect more general problems of the structural hypothesis. It suggests that the same mechanisms (i.e. the same communication channels) are used for both memory saving and memory retrieval. Because structural plasticity is an inherent property of synapses, one would expect that multiple recalls of the same memory should continue to modify the synaptic connections, eventually leading to memory erosions. In addition, further modifications of synaptic connections might occur because the same neurons participate in various neural ensembles and as a result of the spontaneous neuronal activity. The latter difficulty of the hypothesis have been emphasized by Eccles: 'The simple concept that disuse leads to regression of spine synapses and excess usage to hypertrophy can be criticized because…almost all cells…are discharging continuously. One can imagine therefore that there would be overall hypertrophy of all synapses under such conditions…Evidently frequent synaptic excitation could hardly provide a satisfactory explanation of synaptic changes involved in learning.' [4]

Unlike the structural hypothesis, the chemical hypothesis suggests that acquired information is stored within individual neurons at the level of modified molecules, such as altered genes [5], and that new proteins produced by

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