INTRODUCTION

In this thesis I will describe how the development of tools for characterizing the output signals of the primary olfactory processing center made it possible to elucidate some basic principles of odor processing in the honeybee. The results of my thesis are discussed against the background of current knowledge about olfaction; they fill an important gap in the analysis of the olfactory code.

Almost all organisms respond to chemicals in their external environment. This capability is present in simple, single-celled organisms, such as bacteria and protista, as well as in complex metazoans such as mammals, arthropods and molluscs. Chemoreception provides a large amount of often very specific information about food, danger and conspecifics interested in mating or defending their territory. The chemical senses, in particular the olfactory system, must handle an enormous number of diverse stimuli. This vast stimulus array consists of small, generally volatile, organic compounds with molecular weights between 26 and 300 Daltons (Mori and Yoshihara 1995). The number of different odorant molecules has been estimated at 400,000 for the human olfactory system (Mori and Yoshihara 1995), whereby each odorant generally evokes a singular percept. Slight alterations in the molecular structure can lead to substantial shifts in perceived odor quality (e.g. Laska and Teubner 1999). In addition, most odorants occur in the natural environment as complex blends, increasing the number of possible smells by orders of magnitude. For instance, a jasmine flower emits dozens of odorant molecules with various molecular structures (Mori and Yoshihara 1995). The remarkable capacity of the olfactory system to recognize and discriminate this vast array of odors even at extremely low odor concentrations is only comparable to the immune system, which discriminates innumerable different epitopes on antigen molecules or diverse peptides presented by MHC molecules. How is the olfactory system able to perceive this diverse array of stimuli, which cannot be classified according to their positions along a single dimension such as, for example, wavelengths of light or frequencies of sound?

In recent years, research in olfaction has received a boost following the molecular cloning of olfactory receptor genes in vertebrates (reviewed by Mombaerts 1999) and in insects (Clyne et al. 1999; Vosshall et al. 1999) and the establishment of optical recording methods for visualizing the neural representations of odors in the brain (reviewed by Galizia and Menzel 2001; Kauer and White 2001). Odors are perceived by primary olfactory receptor neurons (RNs). These are located in the nose or other olfactory receptor organs such as the

antennae in insects, and express the olfactory receptors, i.e. the molecular units for detecting odorant molecules. For mammals an estimated number of 1000 different receptor types is expressed (Ressler et al. 1994; Vassar et al. 1994), for insects, in particular *Drosophila*, the olfactory receptor family contains only 61 defined members (Clyne et al. 1999; Vosshall et al. 1999). Each receptor encodes a seven-transmembrane domain protein and is probably expressed by only a single RN type (Mombaerts 1996). The small numbers of olfactory receptors appear to be contradictory to the enormous array of different odorant molecules. But since these receptors have broadly-tuned molecular response profiles (Vareschi 1971; Sicard and Holley 1984; Firestein et al. 1993; Sato et al. 1994; Duchamp-Viret et al. 1999; Malnic et al. 1999; Araneda et al. 2000), the olfactory system adopted a strategy by which each receptor type responds, with different affinities, to a variety of stimuli. A specific feature extraction of each odorant molecule must be performed subsequently by higher processing levels. The striking similarity of RNs in different organisms presumably mirrors the common function of these cells. RNs of all animals serve the same dual function, which is to capture and bind odorant molecules, and then convert or transduce the odor signal into an electrical neural signal. The odor signals of the massive afferent input are then relayed to the first olfactory processing center, the olfactory bulb (OB) of vertebrates or its insect analogue, the antennal lobe (AL). Both the OB and AL are spherical structures and reveal important similarities in terms of anatomical and functional features (Boeckh et al. 1990; Hildebrand and Shepherd 1997). The presence of olfactory glomeruli in virtually all olfactory system studies suggests that these structures have particular significance in olfactory processing. Glomeruli are discrete neuropil structures which have been described as one of the most distinctive structures in the brain (Shipley and Ennis 1996). In various animals, the number of glomeruli ranges from 43 in fruit flies (Laissue et al. 1999), and 160 in honeybees (Flanagan and Mercer 1989; Galizia et al. 1999a) to around 2000 - 3000 in mice and rats (reviewed by Shipley and Ennis 1996). They are confined to a superficial layer of the OB or AL and represent structural and functional processing units (Christensen and White 2000).

Using genetically transformed animals, it has been shown that RNs expressing the same olfactory receptor type converge onto single glomeruli in vertebrates (Ressler et al. 1994; Vassar et al. 1994; Mombaerts et al. 1996) and in *Drosophila* (Gao et al. 2000; Vosshall et al. 2000). This implicates that the response of a particular glomerulus is determined by the odor response profile of a specific RN type. However, a glomerulus comprises more than just the averaged input from RNs. It contains a highly-ordered synaptic organization including microcircuitry among RNs, local interneurons (LNs) which only branch within this neuropil, and output neurons (mitral and tufted cells in vertebrates or projection neurons (PNs) in insects), which convey the olfactory information to higher order brain centers (reviewed by Mori and Yoshihara 1995; Shipley and Ennis 1996; Hansson and Anton 2000).

Within the OB and AL various intra- and interglomerular synaptic interactions are accomplished, indicating that a substantial part of odor processing already takes place at the level of the primary brain center. Therefore the OB and AL have been the focus of many physiological studies over the last few years to investigate how these structures encode the vast array of odors.

Using single-cell electrophysiological recordings, the temporal response properties of RNs, LNs and PNs to odors have been very well characterized in vertebrates (e.g. Sicard and Holley 1984; Sato et al. 1994; Duchamp-Viret et al. 1999) and in insects (e.g. Vareschi 1971; Christensen et al. 1993; Sun et al. 1993; Müller 1999; Abel et al. 2001; de Bruyne et al. 2001). These methods provide high temporal resolution, but only one neuron can be measured at a time. In order to investigate the spatial component of the olfactory code, different experimental approaches have been used as direct and indirect indicators for neuronal activity to observe simultaneously entire neuron populations in the OB and AL. Experiments using radioactively marked 2-deoxyglucose or c-fos revealed that odors evoke spatially organized activity patterns, consisting of mosaics of activated glomeruli in the OB and AL (reviewed by Galizia and Menzel 2001). However, since these measurements comprise only a single long-lasting odor stimulation in a single animal, they lack the temporal information and the comparison within the animal for different odors. Thus, optical recording methods have been developed to visualize both spatial and temporal aspects of olfactory coding in the *in-vivo* animal during stimulations with various odors. Several studies, using intrinsic signals (Rubin and Katz 1999; Uchida et al. 2000; Belluscio and Katz 2001; Meister and Bonhoeffer 2001), voltage-sensitive dyes (Cinelli et al. 1995; Friedrich and Korsching 1998; Galizia et al. 2000a; Spors and Grinvald 2002) or calcium imaging (Friedrich and Korsching 1997; Joerges et al. 1997; Galizia et al. 1999b; Sachse et al. 1999; Fuss and Korsching 2001; Wachowiak and Cohen 2001; Fried et al. 2002; Wachowiak et al. 2002), have shown that odors are encoded as specific spatio-temporal 'across-glomeruli' patterns. Each odor evokes activity in several glomeruli, whereby each glomerulus participates in the patterns of several odors. The olfactory system has therefore developed a strategy to encode the huge number of odors with a limited number of coding units. It has further been shown that the odor-evoked patterns are symmetrical in the right and left sides of the OB or AL (Galizia et al. 1998; Belluscio and Katz 2001), and species-specific, indicating that the glomerular response profiles are genetically determined (Cinelli et al. 1995; Friedrich and Korsching 1998; Galizia et al. 1999b; Rubin and Katz 1999). Nevertheless, learning experiments combined with functional imaging have found that the odor representations in the OB and AL are not hardwired, but plastic, leading to specific changes in the individual glomerular response strengths after olfactory learning (Johnson et al. 1995; Johnson and Leon 1996; Faber et al. 1999).

So far the optical measurements mainly investigated the glomerular representation of the afferent input (i.e. responses of RNs) to the OB or AL, respectively. Thus, the strategies and mechanisms of the primary olfactory center involved in odor processing, especially in the sharpening of the broadly-tuned RN responses, are only poorly understood. This raises the following question: How do the complex synaptic networks based on intra- and interglomerular computations within this brain area transform the odor responses of RNs? More precisely, how are odors represented in the output neurons compared to the afferent input? In this thesis I have investigated the processing mechanisms involved in olfactory coding using the honeybee *Apis mellifera* as an experimental animal. The honeybee has several advantages for studying olfactory coding. Honeybees have an excellent olfactory discrimination ability (Frisch 1919; Laska et al. 1999), indicating a very sophisticated olfactory system. Moreover, the glomeruli of the honeybee AL, unlike those in vertebrate OBs, can be individually identified based on their specific shape and relative position (Flanagan and Mercer 1989; Galizia et al. 1999a). Thus, odor-evoked activities in the AL can be attributed to identified glomeruli, which allows comparisons between different individuals. Finally, optical recording methods for visualizing the representation of odors in the honeybee brain have been very well established for some time (Galizia et al. 1997; Joerges et al. 1997; Galizia et al. 1998; Faber et al. 1999; Galizia et al. 1999b; Sachse et al. 1999; Galizia et al. 2000a). However, since the calcium- or voltage-sensitive dyes were bath applied to the whole honeybee brain, these measurements could not distinguish between active RNs, LNs and PNs in the AL. Due to the numerical dominance of the RNs, it is assumed that these calcium signals mainly reflect the afferent input to the AL (Galizia et al. 1998). In order to disentangle the cellular components of the calcium signals, I have developed a new method to selectively measure the calcium responses to odors of the AL output neurons (i.e. PNs) which reflects the processed olfactory information. Using this experimental approach, I investigated different aspects of olfactory coding at this processing level which are specified in the following chapters.

I investigated the spatio-temporal response patterns of selectively-stained PNs in the honeybee AL and compared them among individuals (CHAPTER I). Together with previous studies of odor-evoked spatial activity patterns of the afferent input, I could analyze how the AL shapes the olfactory code. Since it has been suggested that inhibitory interactions within the AL are involved in odor processing (Christensen et al. 1993; Sun et al. 1993), I studied the influence of GABA, the inhibitory transmitter of a subgroup of LNs (Schäfer and Bicker 1986), and its receptor antagonist picrotoxin onto the PN responses. These experiments provide information about inhibitory mechanisms and allowed a postulation of a putative AL wiring model. An exciting finding from these pharmacological experiments was the presence of two separate inhibitory networks. This indicates that beside GABA a second inhibitory transmitter must exist in the honeybee's olfactory system. Interestingly, previous

immunocytochemical studies by Bornhauser and Meyer (1997) have shown the existence of a strong population of histaminergic LNs in the honeybee AL. In collaboration with Philipp Peele, Ana Silbering and Marcel Weidert, we investigated the functional role of histamine in odor processing in the honeybee AL (CHAPTER II).

Most odors occur in the natural environment as complex blends. Thus, the relevant odorants must be properly perceived while irrelevant odors are filtered out of the signal. Therefore a goal of any work with the olfactory system must be to understand the physiological and perceptual effects of odorants in mixtures. Previous calcium imaging experiments in honeybees, which emphasize RN responses, have shown that the representation of binary mixtures included components of both single odors (Joerges et al. 1997; Rappert et al. 1998). However, the response strength of individual glomeruli indicated slight deviations in both positive and negative directions. Due to the inhibitory networks within the AL, one would expect to observe stronger mixture interactions in the PN responses, which have been modified by these networks. Hence, I asked the question how binary mixtures are represented at the output level compared to the representation of their constituent odorants (CHAPTER III). In order to investigate the contributions of the inhibitory networks to the processing of odor mixtures, I analyzed the influence of picrotoxin on the mixture responses.

Behavioral experiments with honeybees indicated that the olfactory system is able to extract the odor quality independently from the intensity of its occurrence (Kramer 1976; Pelz et al. 1997). These findings require a concentration-invariant representation of odors in the AL or higher processing centers. However, previous optical recording studies of honeybee and moth ALs have shown that increasing odor concentrations led to qualitative changes in the odor-evoked activity patterns (Sachse et al. 1999; Galizia et al. 2000b). Therefore I addressed the question whether these changes in quality still persist on the output level or if the odor responses become transformed into a concentration-invariant output pattern. By combining the previously used staining protocol (Galizia et al. 1997) and the selective labeling of PNs, I measured simultaneously the input and output spatio-temporal representation of odors at varying concentrations (CHAPTER IV). In this way I could directly measure how the cellular network of the AL shapes the representation of odors and processes odor quality and intensity.

Optical recording methods are a powerful tool for approaching a lot of different questions. Thus, during my thesis I also contributed to three other projects. In collaboration with Jan Kunze, we optically recorded the neural representation of different odor samples from food-deceptive orchid species (Kunze et al. 2002). Since these species do not offer any reward but still depend on flower-visiting insects, they mimic visual signals of rewarding food plants in order to draw foraging insects to their own, empty, flowers. We analyzed whether these flowers also extended their mimicry to the olfactory floral signals and found no evi-

dence for olfactory mimicry for this orchid species. In addition, I also contributed to the establishing of optical recording methods in the moth, *Heliothis virescens* (Galizia et al. 2000b), and the fruit-fly, *Drosophila melanogaster* (Fiala et al. 2002), in investigating the coding principles of the AL in other insect species. These projects are not included in this thesis.

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