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[REVIEW]

Synaptic Mechanisms Underlying Pheromonal Memory in Vomeronasal System

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ABSTRACT—When female mice are mated, they form a memory of the pheromonal signal of the male with which they mated. Our research objective was to determine the neural mechanisms underlying learning and memory by employing a convenient model of pheromone-induced olfactory memory (pheromonal memory). Formation of pheromonal memory depends on the association between mating and exposure to pheromones. Synaptic plasticity involving this memory occurs in the accessory olfactory bulb (AOB), depending on vaginocervical stimulation at mating. The vaginocervical stimulation at mating reduces the dendrodendritic feedback inhibition of principal neurons (mitral/tufted (MT) cells) in the AOB and enhances their cell activity. The enhancement of activity induces on these plastic changes in dendrodendritic synapses, which in turn enhance GABA-mediated inhibition of MT cell activity. This "self-inhibition" of MT cells activity in response to pheromonal signals of the partner can disrupt its signals at the AOB thereby preventing the signals from reaching the central brain. The formation and maintenance of pheromonal memory is based on this inhibition mechanism.

Key words: postsynaptic density, accessory olfactory bulb, reciprocal synapse, plasticity

Bruce effect and pheromonal memory

When a female mouse is exposed to an unfamiliar (strange) male during her postmating period, she fails to carry on her pregnancy and soon returns to estrus (Bruce, 1959) (Fig. 1). This pregnancy blockade, called the Bruce effect, is mediated by urinary pheromones of the unfamiliar male mouse. However, this is not the case for the male with which the female had mated (male partner). The urinary pheromones of the male partner have the capacity to block pregnancy but do not block a female partner's pregnancy. It was postulated that a female mouse can memorize specific pheromones of her male partner during the critical period after mating. The process of pregnancy is not disturbed by the pheromones of a partner male. Thus, the Bruce effect was thought to be a very useful model to study the pheromone-induced olfactory memory (pheromonal memory) (Brennan *et al*., 1990, Kaba and Nakanishi 1995). On the other hand, the vomeronasal system has an important role in the processing of pheromonal information (Halpern, 1987). The vomeronasal system consists of the vomeronasal organ (VNO) in which the pheromones are perceived, the accessory olfactory bulb (AOB), medial parts of the amygdala including the medial amygdaloid nucleus, and the preoptic area of the hypothalamus (Fig. 2). Pheromonal information is transmitted via the AOB and the amygdaloid nucleus to the hypothalamus, and disturbs the reproductive neuroendocrine function that is necessary for the maintenance of pregnancy (Keverne, 1983; Kaba and Nakanishi, 1995; Brennan and Keverne, 1997; Brennan, 2001; Keverne, 2002). Our research objective was to analyze the synapse mechanisms in the vomeronasal system underlying pheromonal memory.

Several features of the neural basis of the Bruce effect were demonstrated. (1) Memory formation depends on vaginocervical stimulation at mating, but requires a prolonged exposure of 4 to 6 hr to male pheromones immediately after mating (Keverne, 1983; Kaba and Nakanishi, 1995). Exposure to male pheromones alone is insufficient to produce a memory. (2) It was demonstrated that the memory is stored in the AOB (Kaba *et al*., 1989). During the critical period for memory formation, local infusion of an anesthetic into the

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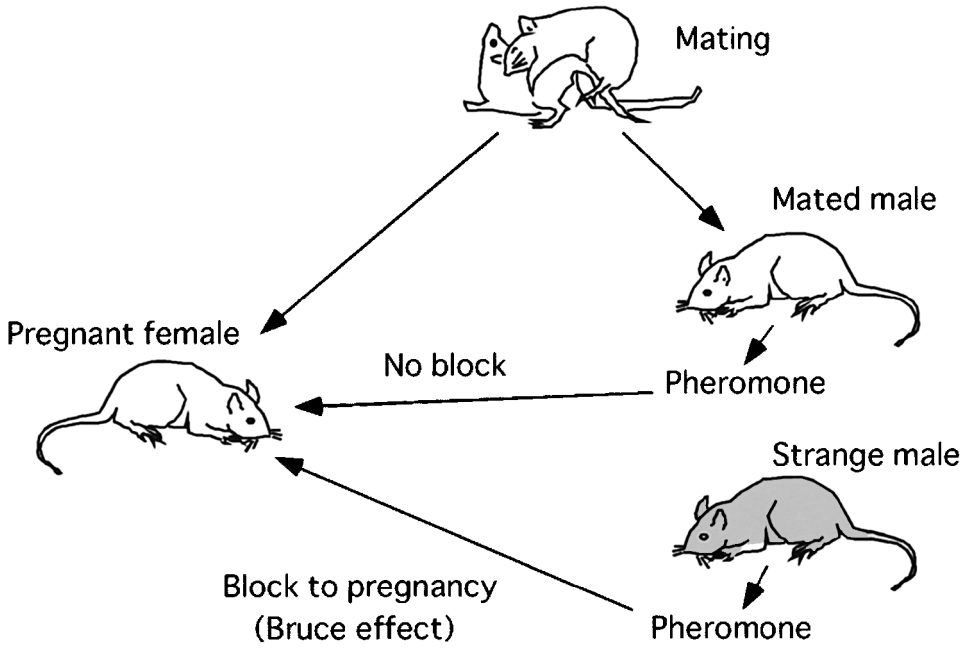


Fig. 1. Bruce effect. When a female mouse is exposed to an unfamiliar (strange) male during her postmating period she fails to carry on her pregnancy. This pregnancy blockade is mediated by urinary pheromones of an unfamiliar male mouse. This is not the case for the mated partner male. (Modified from Kaba and Nakanishi, 1995)

AOB resulted in a memory deficit, while similar treatments on other sites in the vomeronasal pathway did not prevent memory formation. (3) The formation of pheromonal memory depends on mating-induced activation of the noradrenergic system (Rosser and Keverne, 1985; Brennan *et al*., 1995). Destruction of noradrenergic fibers by application of 6-hydroxydopamine disturbs the formation of memory (Rosser and Keverne, 1985). The memory formation depends on noradrenergic innervation of the AOB (Kaba and Keverne, 1992; Rosser and Keverne, 1985). Kaba and Nakanishi (1995) postulated that an essential component of pheromonal memory formation is localized in the neuronal circuit of AOB. (4) Pheromonal memory lasts for at least 30 days following mating (Kaba *et al*., 1989). These characteristic features indicate that pheromonal memory is a good model for studying long-term memory.

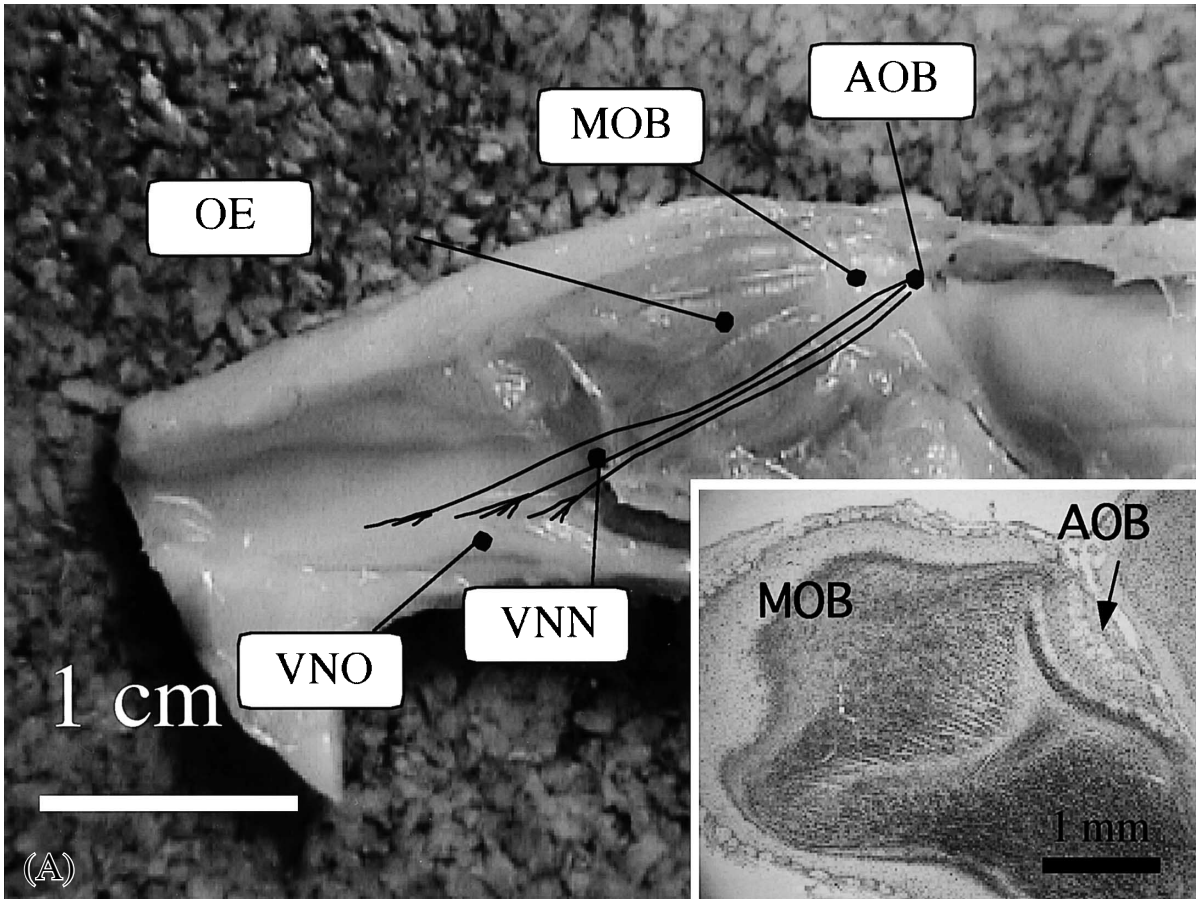
Although synaptic plasticity is regarded as the morphological basis of the long-term memory, no useful model system for investigating the relationship between structural changes and long-term memory formation is available to date. We have attempted to analyze the neural mechanisms underlying learning and memory by employing a convenient model of pheromonal memory in the vomeronasal system. Thus, I will review the synaptic mechanism of pheromonal memory. This review is expected to be useful not only for researchers of the olfactory system but also for those who are interested in learning and memory.

Neuronal circuits mediating pheromonal memory

The neuronal circuit of AOB plays a central role in formation of pheromonal memory (Kaba *et al*., 1989, Brennan, 1990). Axons of vomeronasal receptor cells reach the dorsal surface of the AOB to form synaptic contacts with the dendrites of principal neurons (mitral/tufted (MT) cells) in the glomeruli (Fig. 3). Axons of MT cells project to higher centers in the vomeronasal system. On the other hand, MT cell dendrites form special dendrodendritic synapses, so-called reciprocal synapses, with interneurons (granule cells) (Ichikawa, 1996; Matsuoka *et al*., 1998).

The reciprocal synapse consists of a pair of excitatory (asymmetrical) and inhibitory (symmetrical) synapses (Fig. 3). Fig. 4 shows an electron micrograph of the reciprocal synapse. The asymmetrical synapse in which the MT cell dendrite is presynaptic, has a prominent postsynaptic density (PSD) whereas the symmetrical synapse in which the granule cell dendrite is presynaptic, has symmetrical pre- and postsynaptic densities. The former is a glutamatergic excitatory synapse and the latter is an inhibitory GABAergic synapse. When dendrites of MT cells are activated by vomeronasal nerve impulses, they then depolarize adjacent granule cell dendrites by releasing an excitatory synaptic transmitter (glutamate) at asymmetrical synapses. The depolarized granule dendrites in turn release an inhibitory synaptic transmitter (GABA) at symmetrical synapses and hyperpolarize MT cell dendrites (Taniguchi and Kaba, 2001). This GABA-mediated feedback inhibition system in the reciprocal synapse has been thought to be the most important regulatory means of controlling the outflow from the AOB to higher brain centers (Kaba and Nakanishi, 1995; Ichikawa, 1996; Brennan and Keverne, 1997).

Noradrenergic fibers mediating the mating-induced activation innervate into the AOB (Kaba and Keverne, 1992;



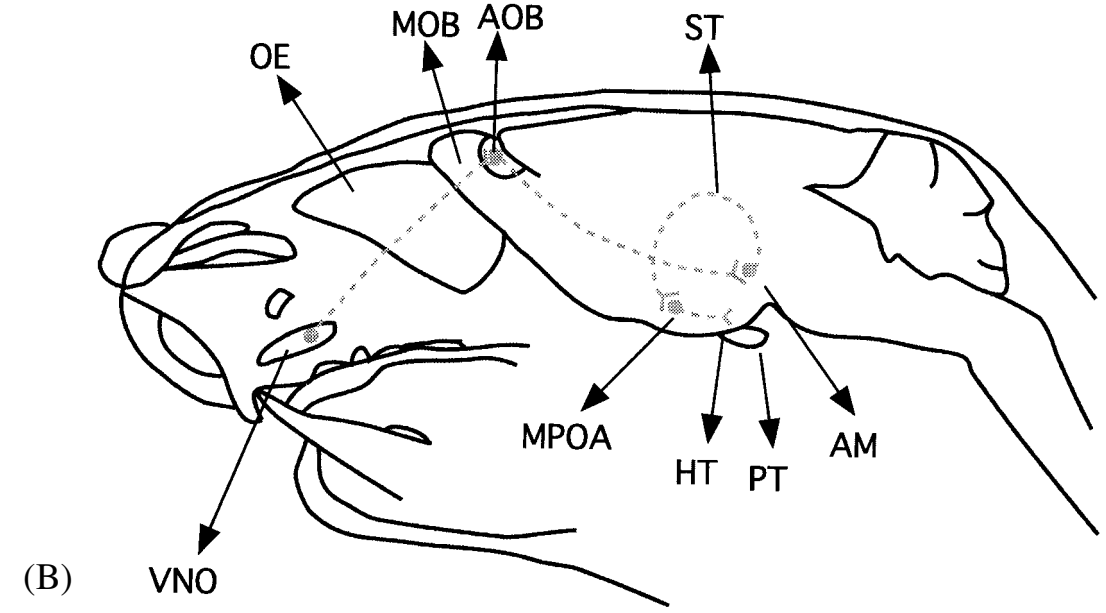


Fig. 2. (A) Photograph shows two olfactory systems; main olfactory system (OE, olfactory epithelium; MOB, main olfactory bulb) and vomeronasal system (VNO, vomeronasal organ; VNN, vomeronasal nerve; AOB, accessory olfactory bulb). Inset shows a sagittal section of the olfactory bulb. (B) A sagittal representation of vomeronasal system. Vomeronasal system consists of vomeronasal organ (VNO), accessory olfactory bulb (AOB), medial parts of amygdala (AM) including medial amygdaloid nucleus, and preoptic area of hypothalamus (MPOA). ST, stria terminalis; HT, hypothalamus; PT, pituitary; OE, olfactory epithelium; MOB, main olfactory bulb.

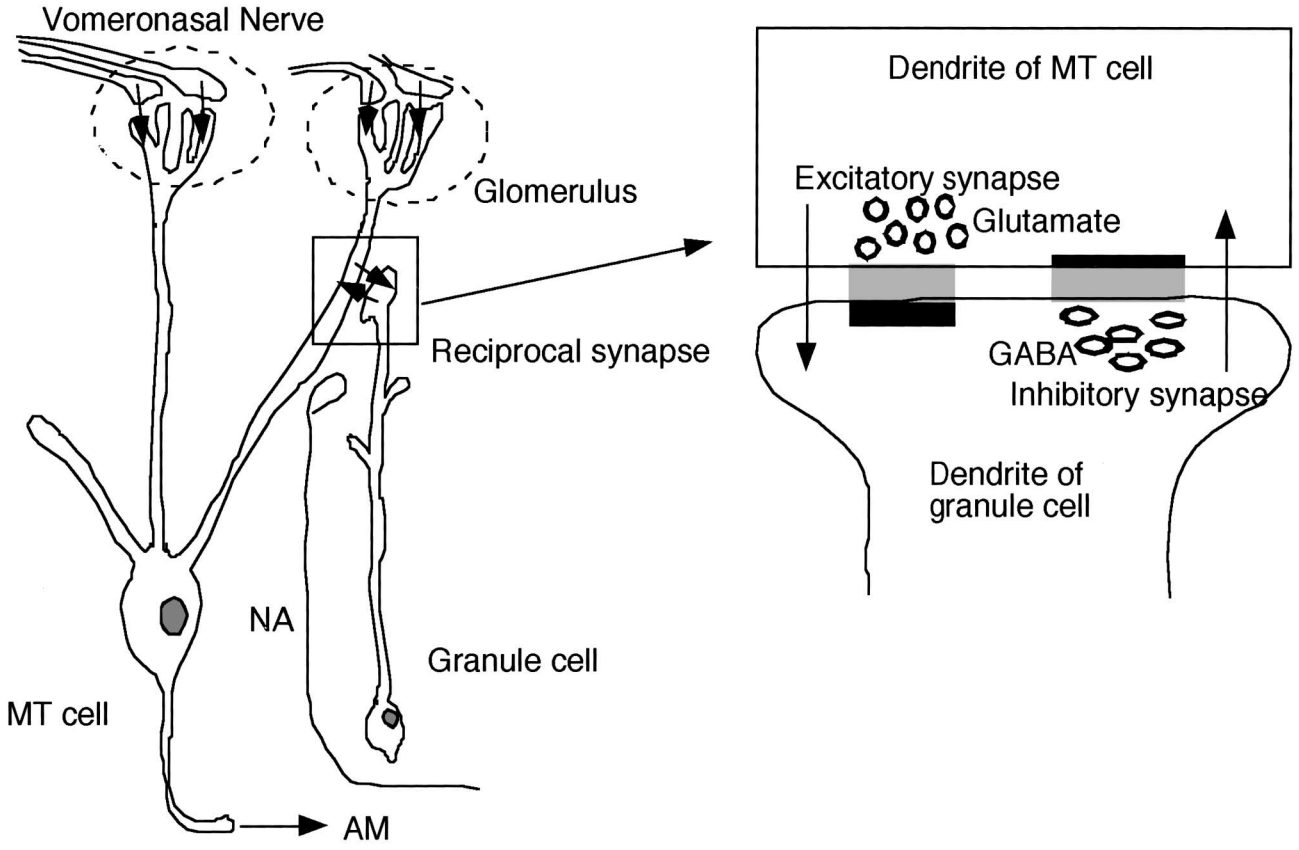


Fig. 3. Diagram of neuronal circuits in the AOB. Vomeronasal nerves form synaptic contacts with dendrites of MT cells in the glomeruli. The MT cells project to higher centers of the vomeronasal system, such as medial amygdala (AM). MT cell dendrites form special dendrodendritic synapses, called reciprocal synapses, with granule cells. The reciprocal synapse consists of a pair of excitatory (asymmetrical) and inhibitory (symmetrical) synapses.

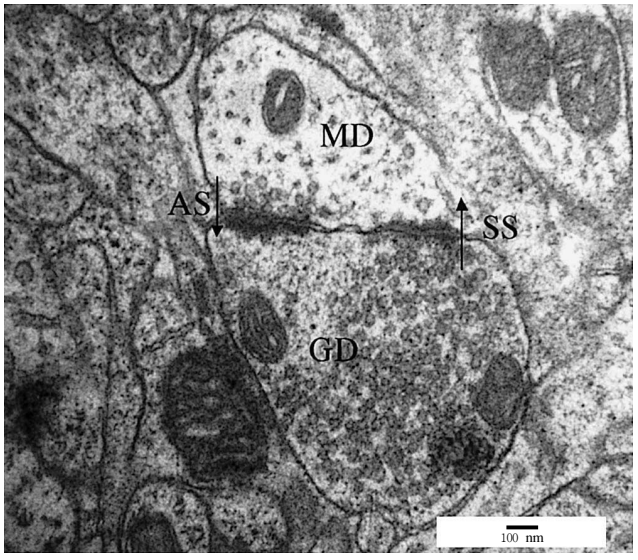


Fig. 4. Electron micrograph of reciprocal synapse. MD, dendrite of MT cell; GD, dendrite of granule cell; AS, asymmetrical synapse; SS, symmetrical synapse. Arrows indicate the direction of synapse.

Rosser and Keverne, 1985). However, it is not clarified what kinds of neurons receive the terminals of noradrenergic fibers in the AOB.

Vaginocervical stimulation and noradrenergic system

Formation of pheromonal memory depends on the association between mating and exposure to pheromones. The main information of mating is thought to be vaginocervical stimulation (VCS). The effects of VCS on MT cells of AOB were examined (Otsuka *et al*., 2001). The paired-pulse depression of MT cell by stimulation of MT cell's axons is considered to be due to feedback inhibition of MT cells from granule cells via reciprocal dendrodendritic synapses. Artificial vaginocervical stimulation reduced paired-pulse depression of amygdala-evoked field potentials recorded in the AOB and enhanced the single-unit activity of MT cells antidromically stimulated from the amygdala. These findings suggest that VCS at mating reduces the dendrodendritic GABA-mediated inhibition of MT cells and enhances the activity of MT cells.

Artificial VCS or mating promotes noradrenaline release in the AOB (Rosser and Keverne, 1985; Brennan *et al*., 1995). Removal of noradrenergic innervation of the AOB prior to

mating and blockade of alpha-adrenergic receptors in the AOB immediately after mating prevent the formation of pheromonal memory (Rosser and Kevern, 1985; Kaba and Kevern, 1988). Terminations and synaptic contacts of noradrenergic fibers, however, remain to be elucidated. Recently we have examined the localization of terminals of noradrenergic fibers and adrenergic receptors using immunocytochemistry and *in situ* hybridization (Takigami *et al*., 2003). Using electron microscopy, immunoreactivities for dopamine beta hydroxylase (DBH), a synthetic enzyme for noradrenaline, in neuronal terminals were observed around MT cells. *In situ* hybridization and immunocytochemistry for alpha 2c noradrenergic receptors revealed that the receptors are expressed in MT cells but not in granule cells. These results suggest that noradrenaline has an effect on MT cells and reduces the GABA-mediated inhibition at mating. Consequently, at mating, the excitation of MT cells, which is activated simultaneously by pheromones of the partner, is enhanced strongly by a release of noradrenaline in the AOB and induces the formation of pheromonal memory.

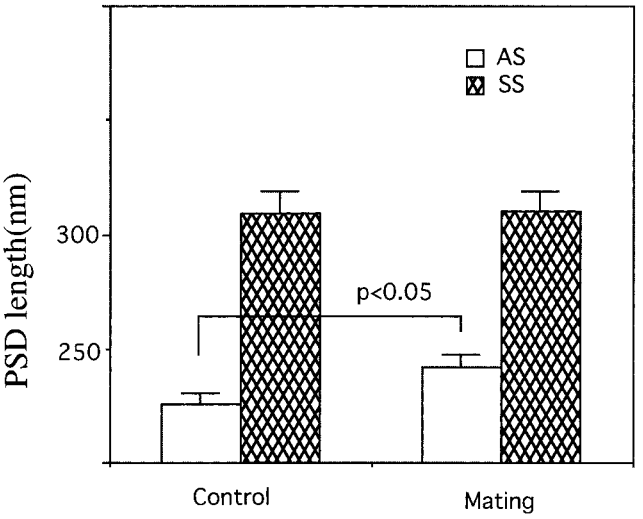


Fig. 5. PSD size of reciprocal synapse. PSD size of asymmetrical synapse is larger in the mating group than in control group. AS, asymmetrical synape; SS, symmetrical synapse.

Synaptic plasticity in formation of pheromonal memory

Generally, it is agreed that a memory can be encoded by activity-dependent changes in the structure or strength of synapses (Bailey and Kandel, 1993; Bliss and Collingridge, 1993; Luscher *et al*., 2000; Malenka and Siegelbaum, 2001; Martin *et al*., 2001). After induction of long-term potentiation, which is one of the best models of learning and memory, various morphological changes of synapses were demonstrated in the hippocampus (Fifkova and Van Harreveld, 1977; Toni *et al*., 1999; Klintsova and Greenough, 1999). Similarly, to investigate such synaptic plasticity underlying memory formation, the AOB is thought to be a useful model due to its simple and interesting circuitry (Brennan, 1997, 2001).

It was suggested that the activity of MT cells in the AOB of female mice is enhanced transiently at mating (Otsuka *et al*., 2002). Thus, we examined whether morphological changes occur in AOB synapses upon association between mating and pheromonal exposure (Matsuoka *et al*., 1997). Female mice were divided into two group: female mice of the mating group were mated with a male partner and left in the presence of the partner's pheromones (soiled bedding of the partner male) for 6 hr before removal of the soiled bedding by cleaning the cage, whereas the other females of the control group were exposed to male pheromones in the soiled bedding for 6 hr without mating. The PSD size of glomerular and reciprocal synapses were measured under an electron microscope. Figure 5 shows that the PSD size of asymmetrical synapses in reciprocal synapses was significantly larger in the mating group than in the control group (Matsuoka *et al*., 1997). There was no significant difference in the PSD size of symmetrical synapses in reciprocal synapses and glomerular synapses between the mating group and control group. The enlargement in the size of PSD is thought to be accompanied by the increase in the number of receptors. It was hypothesized that newly synthesized receptors are in clusters and are transferred to synapses, then the clusters fuse at postsynaptic sites depending on activation (Sheng and Kim, 2002). Indeed, the clusters of various receptors, for example NMDA receptor subtype NR1, AMPA type receptor subtype GluR1 and GABAa receptor were observed in dendrites *in vitro*, and the structure or localization of these clusters is regulated by neuronal activities (See reviews: Craig and Boudin, 2001; Sheng, 2001; Carroll and Zukin, 2002; Song and Haganir, 2002). It was reported that the GABA level in the AOB is higher after the formation of pheromonal memory than before (Brennan *et al*., 1995). These findings suggest that the GABA-mediated feedback inhibition is reinforced after the mating (Fig. 6). The enhancement of GABA-mediated inhibition in MT cells in response to the pheromonal signals of mating male can disrupt its signals at the AOB. Taking together all these data, the following is hypothesized. The transient enhancement of MT cell activity at mating induces the plastic changes of asymmetrical synapses in reciprocal synapses, which in turn induce enhancement of GABA-mediated inhibition. This "self-inhibition" is a basic mechanism underlying formation of pheromonal memory. An increment of the self-inhibition disrupts the pheromonal signals of the partner at the AOB and prevents the signals from being transmitted centrally to induce pregnancy blockade (Kaba and Nakanishi, 1995; Ichikawa, 1996; Brennan and Keverne, 1997).

Synaptic mechanisms of long-term memory

The pheromonal memory lasts for about one month following mating unless a pregnancy ensues (Kaba, 1988). To investigate the long-term maintenance of pheromonal memory, we examined the plastic changes of reciprocal synapses using electron microscopy in the short-term period after memory formation (1, 3 and 5 days after mating), the

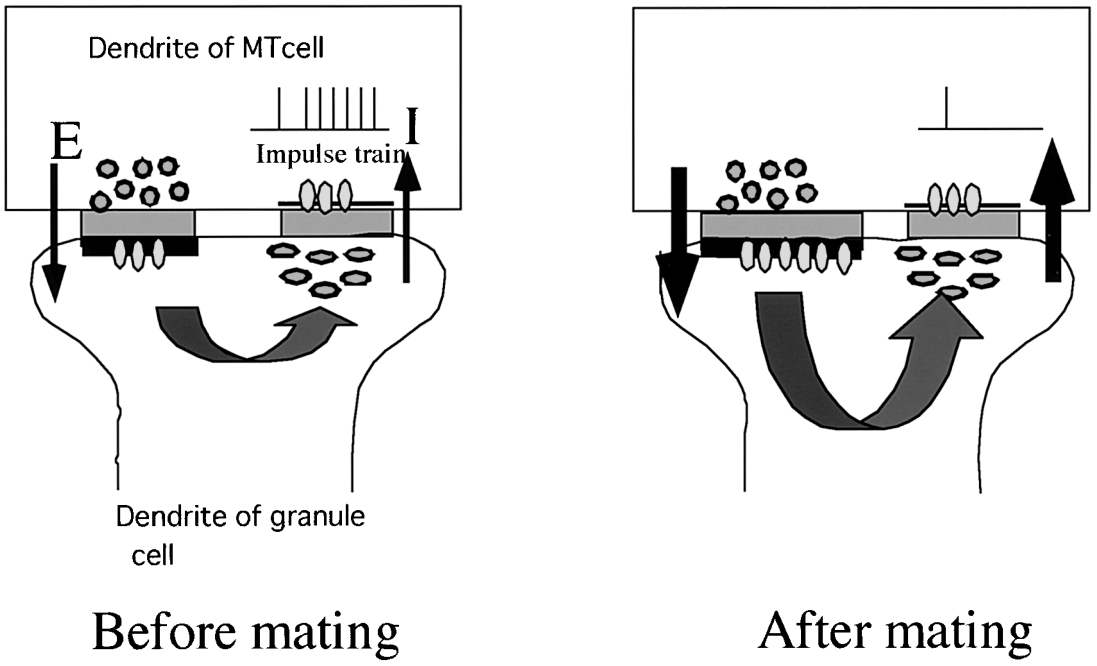


Fig. 6. GABA-mediated feedback inhibition in the reciprocal synapse. This inhibition is enhanced after mating. E, excitation; I, inhibition.

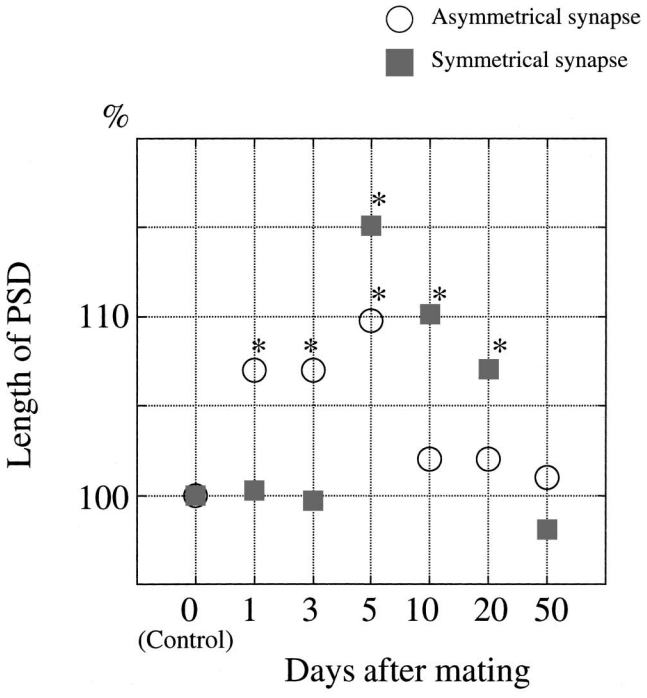


Fig. 7. Long-term changes of the PSD size of excitatory (asymmetrical) and inhibitory (symmetrical) synapses in the reciprocal synapses of the female mice AOB after mating (%). The asterisks indicate the statistically significant differences from the control values.

long-term maintenance period (10 and 20 days after mating) and the time of fading of this memory (50 days after mating)(Matsuoka *et al*., 2003). The modification of excitatory asymmetrical synapses was observed 1, 3 and 5 days after mating, in contrast, that of inhibitory symmetrical synapses was observed 5, 10 and 20 days after mating (Fig. 7). These continuous morphological changes make it possible to maintain the long-term GABA-mediated inhibitory effect on MT cells. This cascade of modification in different types of synapse is the basis of long-term memory formation and maintenance (Fig. 8). Fifty days after mating, both asymmetrical and symmetrical synapses in reciprocal synapses did not show any modification. This result is in accordance with a report that the pheromonal memory lasts for about one month. It is not clarified what mechanism is involved in the transformation of synaptic plasticity from an excitatory synapse to an inhibitory synapse in reciprocal synapses. The modification of both the excitatory and the inhibitory synapses will inhibit the activity of MT cells in the long term. The long-term inhibition of MT cell activity must be based on the long-term memory (Fig. 8).

Synaptic mechanisms underlying formation of pheromonal memory

Connection between vomeronasal receptor neurons and MT cells

To explain the Bruce effect, we should suggest one hypothesis as follows. Individual MT cells in the AOB receive specific (single) input from vomeronasal receptor neurons. It is well known that the principal neurons (mitral cells and tufted cells) in the main olfactory bulb establish specific neuronal connections with olfactory receptor neurons. Each receptor neuron in the olfactory epithelium carries only one type of olfactory receptor (one cell-one receptor rule; Russler *et al*., 1993; Vassar *et al*., 1993). An olfactory receptor neuron expressing the same olfactory receptor projects to a single/ a few glomeruli in the main olfactory

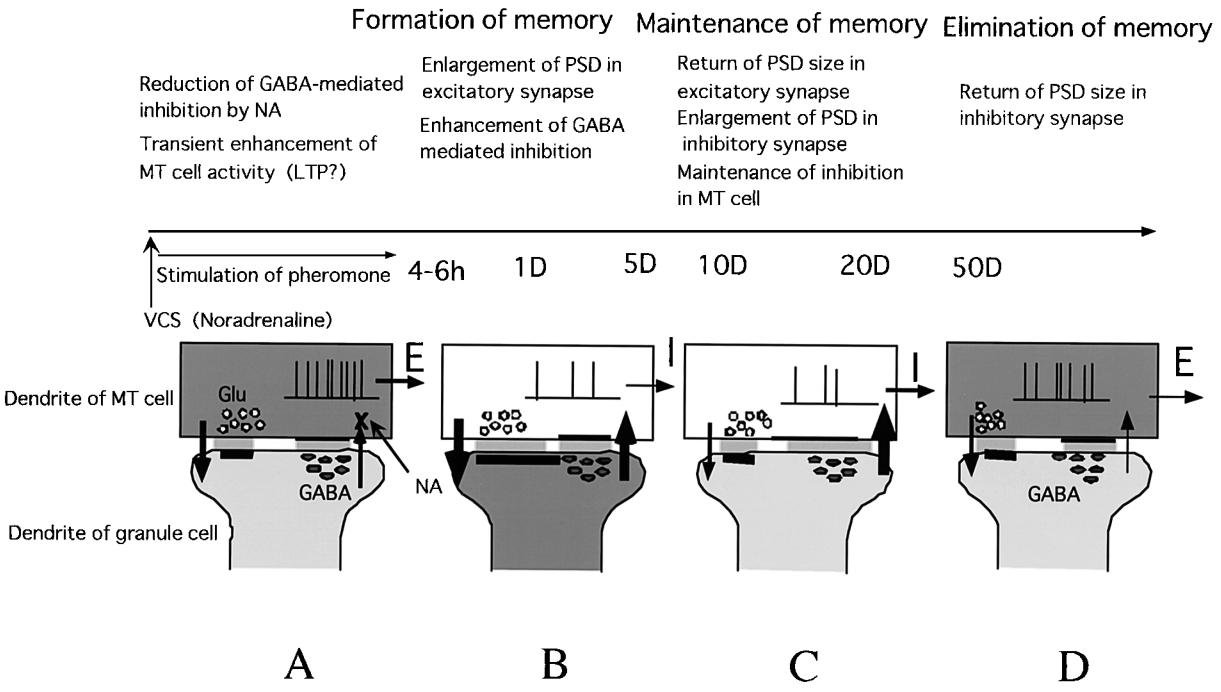


Fig. 8. Hypothetical representation of synaptic mechanisms underlying long-term pheromonal memory. Each diagram shows the mechanism at mating (A), short-term period (B), long-term period (C), and time of fading of memory (D). NA, noradrenaline; VCS, vaginocervical stimulation; E, excitation of activity; I, inhibition of activity.

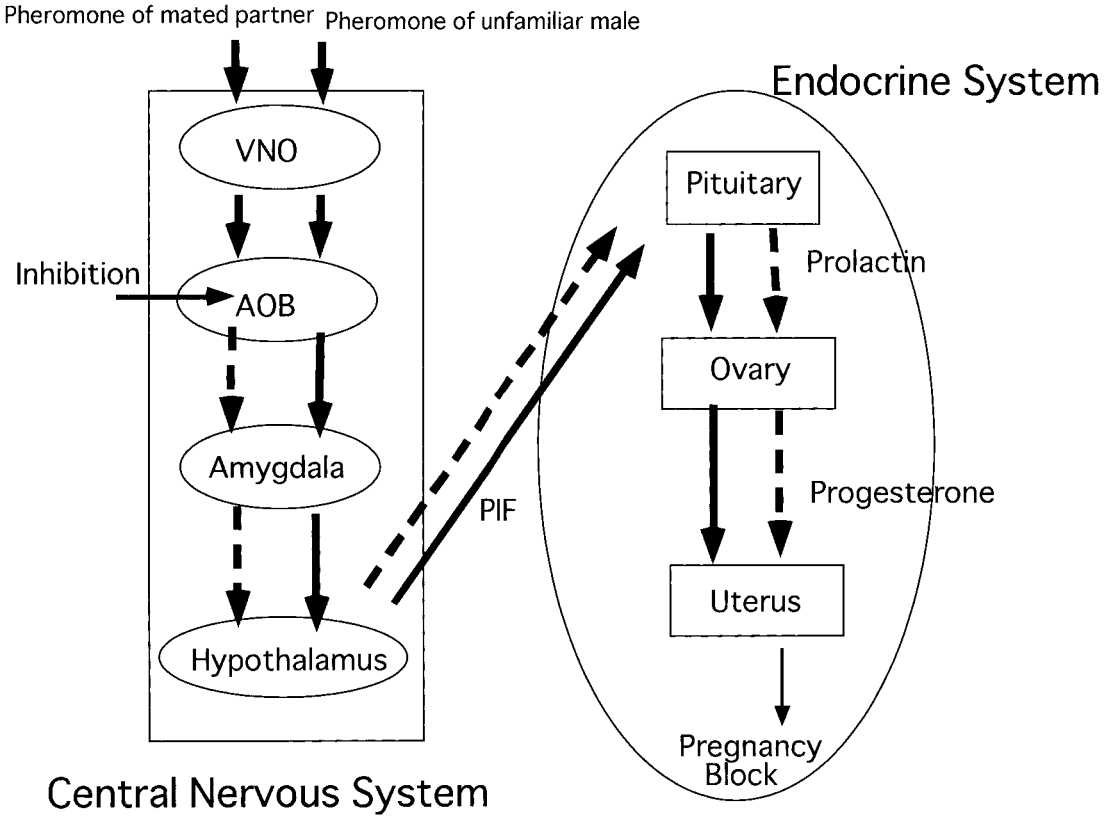


Fig. 9. Mechanisms of Bruce effect. Left flow shows the effect of pheromone of the male partner. Right flow shows the effect of pheromone of an unfamiliar male (Bruce effect). Broken arrows indicate inhibition or modification of informations.

bulb, the first center of the olfactory system. In the glomeruli, the axons form excitatory synapses with dendrites of mitral and tufted cells, the principal neurons in the main olfactory bulb (Mombaert *et al*., 1996; Mori and Yoshihara, 1995). A principal neuron projects its single primary dendrite to one glomerulus (Mori, 1987), to receive information from only one olfactory receptor. The single principal neuron may serve as only one coding module for many odorants. The fine connection between vomeronassal receptor neurons in VNO and the principal neurons in the AOB has not been clarified yet. Recent studies indicate a high possibility of the hypothesis that each principal neuron would receive information from a given receptor type in the vomeronasal system (Rodrigeuz *et al*., 1999; Brennan, 2001; Punta *et al*., 2002).

Mechanism of the Bruce effect

If, in the vomeronasal system, each principal neuron in the AOB receives the input of one or a few receptor types, only the principal neurons that received the pheromonal information of the parter at mating will show synaptic plasticity. If this is the case, we can explain the Bruce effect as follows. After the mating, the neurons that received the pheromonal information of a partner can inhibit the information (Fig. 9). The female is able to maintain her pregnancy. On the other hand, the other neurons that receive the pheromonal information from an unfamiliar (strange) male had not exhibited any synaptic plasticity. If these neurons received the phermonal information from an unfamiliar male, the neurons were not inhibited in the AOB and would send the information to higher centers. When the hypothalamus receives the pheromonal information, the endocrine system, which preserves the pregnancy, is disturbed by the pheromonal information and fails to maintain the pregnancy (Fig. 9). When a mated female is exposed to a pheromone of an unfamiliar male, the pheromone induces the release of prolactin inhibitory factor from the hypothalamus. In the pituitary, the release of prolactin is inbibited by the effect of prolactin inhibitory factor and then the release of progesterone from ovary is also inhibited. As the final effect, the pregnancy blocked, that is, the Bruce effect. Thus, enhancement of GABA-mediated inhibition by synaptic plasticity has an important role in the formation of pheromonal memory.

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