Chapter 3

Hippocampal Function and Gonadal Steroids

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1. Introduction

The hippocampus plays a central role to form new episodic memory in various species including humans (Scoville and Milner, 1959). The hippocampal neurons seem to process variety of information, such as spatial location (Wills et al., 2010), temporal information (Mitsushima et al., 2009), and emotional state (Chen et al., 2011) within specific episodes (Komorowski et al., 2009; Gelbard-Sagiv et al., 2008). However, the critical mechanism how to sustain a piece of specific memory and how to organize the memory fragment to form "episodes" is still largely unknown.

Since selective blockade of long-term potentiation (LTP) induction by NMDA receptor antagonist impairs hippocampal learning (Morris et al., 1986), LTP has been considered as a cellular model of hippocampal memory (Bliss and Lømo, 1973). In 2006, *in vivo* field EPSC recording study showed that hippocampal learning induces LTP in CA1 region of hippocampus (Whitlock et al., 2006). Further, we revealed that learning-dependent synaptic delivery of AMPA receptors into the CA3-CA1 synapses is required for hippocampal learning (Mitsushima et al., 2011). Since there is no tetanus electrode in brain, endogenous trigger and/or the mechanism inducing the learning-dependent LTP were still unknown.

As an endogenous trigger of LTP, we hypothesized acetylcholine (ACh) release in the hippocampus that increases during learning or exploration in freely moving animals. In fact, without electrode for tetanus stimulation, bath treatment of ACh agonist not only induces specific bursts (Fisahn et al., 1998) but also forms LTP in CA1 region of hippocampal slices (Auerbach and Segal 1996). Moreover, bilateral intra-hippocampal treatments of muscarinic receptors impair hippocampal learning (Herrera-Morales et al., 2007; Rogers and Kesner 2004). In this review, we focused on *in vivo*ACh release in the hippocampus in order to improve our understanding of sex specific and steroids-dependent mechanism of hippocampal function.

2. Role of ACh in the hippocampus

A number of studies suggest that AChplays an important role in orchestrating major hippocampal functions (Fig. 1). In behavioural studies, ACh release increases during learning (Ragozzino et al., 1996; Stancampiano et al., 1999; Hironaka et al., 2001) and is positively correlated with learning performance (Gold, 2003; Parent and Baxter, 2004). Bilateral injections of scopolamine into the dorsal hippocampus impair spatial learning ability (Herrera-Morales et al., 2007), suggesting that muscarinic ACh receptors mediate the formation of spatial memory. At the network level, ACh generates a theta rhythm (Lee et al., 1994) that modulates the induction of long-term potentiation (LTP) in hippocampal CA1 neurons (Hyman et al., 2003). Studies exploring a genetic deficiency of muscarinic ACh receptors (M_1or M_2) further show the impairment of LTP in the CA1 region (Seeger et al., 2004; Shinoe et al., 2005). At the cellular level, both pyramidal and non-pyramidal neurons in the hippocampal CA1 area receive direct cholinergic afferents mediated by muscarinic receptors (Cole and Nicoll, 1983; Markram and Segal, 1990; Widmer et al., 2006). *In vitro* studies showed that bath application of carbachol, a cholinergic agonist, induces LTP in CA1 pyramidal neurons without electrical stimulus, suggesting that ACh in the hippocampus plays a principal role in the synaptic plasticity of the CA1 pyramidal neurons (Auerbach and Segal, 1996). Furthermore, a recent study revealed an intracellular mechanism of ACh: focal activation of muscarinic ACh receptors in one CA1 pyramidal neuron induces Ca^{2+} release from inositol 1,4,5-trisphosphate-sensitive stores to induce LTP (Fernández de Sevilla, 2008).

Not only is ACh critically involved in synaptic plasticity, ACh release in the hippocampus is also responsible for neurogenesis in the dentate gyrus. Thus, neurotoxic lesions of forebrain cholinergic neurons or long-term scopolamine treatment significantly decreases the number of newborn cells in the dentate gyrus, approximately 90% of those were also positive for the neuron-specific marker NeuN (Mohapel et al., 2005; Kotani et al., 2006).

3. Monitoring of in vivoACh release

Cholinergic neurons within the basal forebrain provide the major projection to the neocortex and hippocampus (Mesulam, et al., 1983). Cortical regions receive cholinergic inputs mainly from the nucleus basalismagnocellularis(NBM) or the diagonal band of Broca, whereas the hippocampus receives cholinergic inputs mostly from the medial septum and horizontal limb of the diagonal band of Broca (Mesulam, et al., 1983). Because the cholinergic projections are necessary to maintain learning and memory (Perry et al., 1999, Sarterand Parikh, 2005), we hypothesized that *in vivo* monitoring of ACh release in the hippocampus is necessary to elucidate learning function. To measure ACh release, we have performed *in vivo* microdialysis studies in freely moving rats. Briefly, a microdialysis probe with a semipermeable membrane (1.0 mm in length) was inserted into a specific brain area via a surgically pre-implanted guide cannula. We perfused the inside of the membrane with artificial cerebrospinal fluid, and assayed ACh in dialysates using a high-performance liquid

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chromatography system. As a result, we were successful in determining an *in vivo* ACh release profile in selected brain areas in freely moving rats (Figure 2).

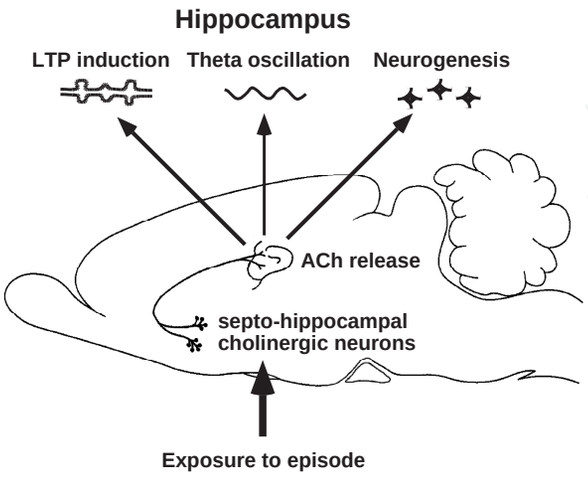

Figure 1. Schematic illustration of septo-hippocampal cholinergic neurons in rats. Exposure to episode induces ACh release in the hippocampus that activates hippocampal functions. Scopolamine induces amnesia in many mammalian species, including humans. For example, many people remember where they were and what they were doing when serious events occur. ACh, acetylcholine. LTP, long-term potentiation.

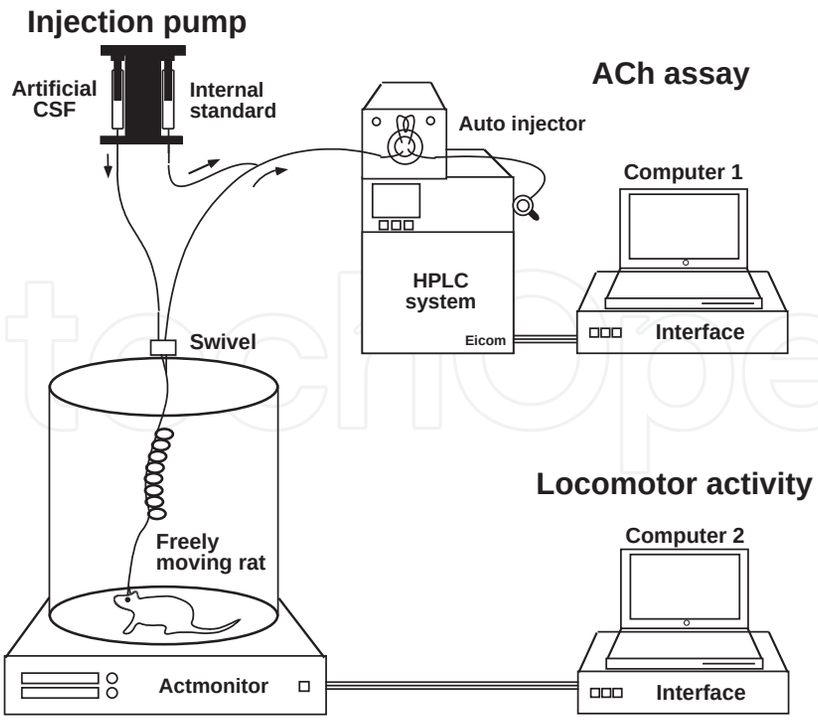

Figure 2. Experimental setup of *in vivo* microdialysis system. We examined *in vivo* ACh release and spontaneous locomotor activity in the same subject.

4. Sex differences inACh release

We first reported sex-specificACh release in the hippocampus in 2003 (Mitsushima et al., 2003). Gonadally intact male rats consistently show a greater ACh release in the hippocampus compared with diestrous or proestrous female rats, suggesting a sexually dimorphic septo-hippocampal cholinergic system. Moreover, we found that sex-dependent ACh release also shows a time-dependent 24-h profile: ACh release in the hippocampus was relatively similar in the light phase, but consistently lower in female compared with male rats in the dark phase (Masuda et al., 2005). Although ACh release clearly showed a daily rhythm in female rats, females exhibited smaller amplitude of daily change than males. However, it is necessary to rule out the possibility that the sex difference in ACh release reflects the differences in spontaneous locomotor activity levels. By simultaneous monitoring of ACh levels and spontaneous locomotor activity, we revealed a real sex difference in the "ACh release property" (Figure 3, Mitsushima et al., 2009): males showed higher ACh release than females while displaying similar levels of behavioural activity. Although female rats showed slightly higher overall spontaneous activity than intact male rats, male rats showed higher ACh release than female rats. Simple linear regression analysis was used to evaluate the relationship between ACh levels and spontaneous locomotor activity (Figure 3). Pearson's correlation coefficient (r) or slope of the best fit line was calculated for each rat, and sex difference was evaluated using ANOVA. We found that the data from intact males had a steeps lope of fit line, while the data from females had a gentle slope. These results suggest that sex-specific ACh release is not due to the change in spontaneous behavior, but due to actual differences in the ACh release property in gonadally intact rats (Mitsushima et al., 2009).

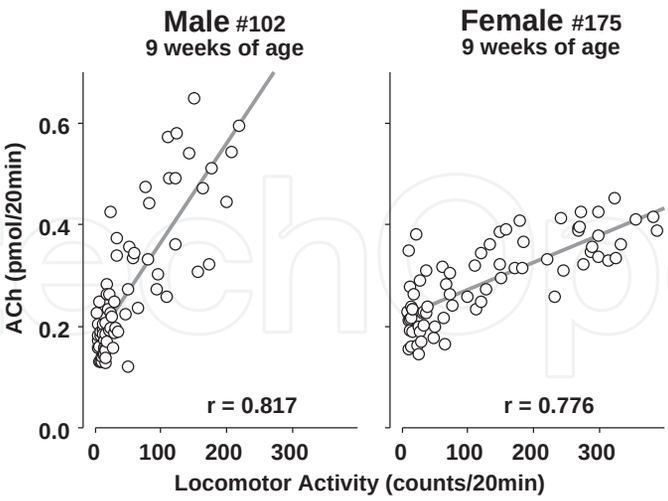

Figure 3. Sex specific ACh release property in behaving rats. Representative data from a male (#102) and a female (#175) rat were shown. Simple linear regression analysis revealed a sex-specific "ACh release property." Male rats showed higher ACh release than females undergoing similar behavioural activity levels. Although both sexes showed a high correlation, male rats showed a steeper slope than female rats in the hippocampus (see Mitsushima et al., 2009). Conversely, in neocortical area, females show higher ACh release and correlation than males (see Takase et al., 2009)

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To evaluate neuroanatomical sex difference in the septo-hippocampal cholinergic neurons, we performed immunocytochemistry. Stereological analysis showed that no sex difference was observed in the number and the distribution of choline acetyltransferaseimmunoreactive(ChAT-ir) cells in the medial septum or horizontal limb of diagonal band (Takase et al., 2009). Since the number of septo-hippocampal cholinergic neurons does not appear to be involved in the sex difference in ACh release in the hippocampus, we hypothesized that sex-specific neural circuits or substance(s) may control the endogenous release.

5. Neural control of septo-hippocampal cholinergic neurons

Neurotransmitters may be involved in expression of the sex difference in ACh release. For instance, dopaminergic neurons in the ventral tegmental area (A10) have been shown to control septo-hippocampal cholinergic neurons through the A10-septal dopaminergic pathway in male rats(Swanson, 1982; Nilsson et al., 1992; Yanai etal., 1993). A neuroanatomical study suggested that dopamine D_2receptors rather than D_1 receptors mediate the dopaminergic control of septo-hippocampal cholinergic neurons (Weiner et al., 1991). It has been shown that opiatergic neurons also control septo-hippocampal cholinergic neurons in male rats (Mizuno and Kimura, 1996); the injection of naloxone, a μ opioid receptor antagonist, into the medial septum markedly increased ACh release in the hippocampus, while a μ opioid receptor agonist decreased its release (Mizuno and Kimura, 1996). In contrast, GABA seems to inhibit septo-hippocampal cholinergic neurons; the injection of muscimol, a GABA receptor agonist, into the medial septum decreased ACh release in the hippocampus, while the injection of bicuculline, a GABA receptor antagonist, increased it (Moor et al., 1998). Although the neural systems are still unknown for female rats, it seems likely that neural control of septo-hippocampal cholinergic neurons is involved in the expression of sex differences in ACh release. It will be important to investigate these neural systems in female rats in future studies.

6. Circulating sex steroids activate ACh release

Not only neurotransmitters, but also circulating sex steroids, may regulate cholinergic neurons. In fact, neuroanatomical studies have demonstrated that, in intact male and female rats, a number of dopaminergic neurons in the A10 region have androgen receptor immunoreactivity (Kritzer,1997) and 45-60% of cholinergic neurons in the medial septum have estrogen receptor α immunoreactivity (Miettinen et al.,2002; Mufson et al., 1999). Taken together with the fact that female rats show a greater circulating estrogen concentration than male rats (Shors et al., 2001; Mitsushima et al., 2003b) and male rats show a greater circulating androgen concentration than female rats (Falvo et al., 1974; Rush and Blake, 1982), it is possible that cholinergic neurons are affected by sex steroids differently in male and female rats.

The activational effects of sex steroids on cholinergic neurons have been suggested by previous neuroanatomical and neurochemical findings. For example, male gonadectomy decreases the density of cholinergic fibers in the dorsal hippocampus, while testosterone replacement in gonadectomized male rats maintains fibre density (Nakamura et al., 2002). Also, estradiol increases the induction of choline acetyltransferase in the basal forebrain in gonadectomized female rats (Luine et al., 1986; McEwen and Alves, 1999). A previous *in vitro* study demonstrated that estradiol treatment increases both high affinity choline uptake and ACh synthesis in basal forebrain neurons (Pongrac et al., 2004). Furthermore, we recently reported an activational effect of sex steroids on the maintenance of stress-induced ACh release in the dorsal hippocampus in immobilized rats (Mitsushima et al., 2008). These findings suggest the activational effect of sex steroids on ACh release in the dorsal hippocampus, and we presented conclusive evidence of activational effects on dynamic ACh changes in behaving animals. To analyze the precise effects of sex steroids on ACh release, we simultaneously analyzed ACh release and spontaneous locomotor activity to determine the precise effect of sex steroids. Simultaneous analysis revealed that gonadectomy severely impaired ACh release without affecting spontaneous locomotor activity levels. Moreover, the activational effect on ACh release was apparent, especially during the active period, ie the dark phase, but not during the rest period, the light phase (Figure 4 and Mitsushima et al., 2009). Our results provide the first evidence that the sex-specific 24-h profile of ACh release is highly dependent on the presence of sex steroids.

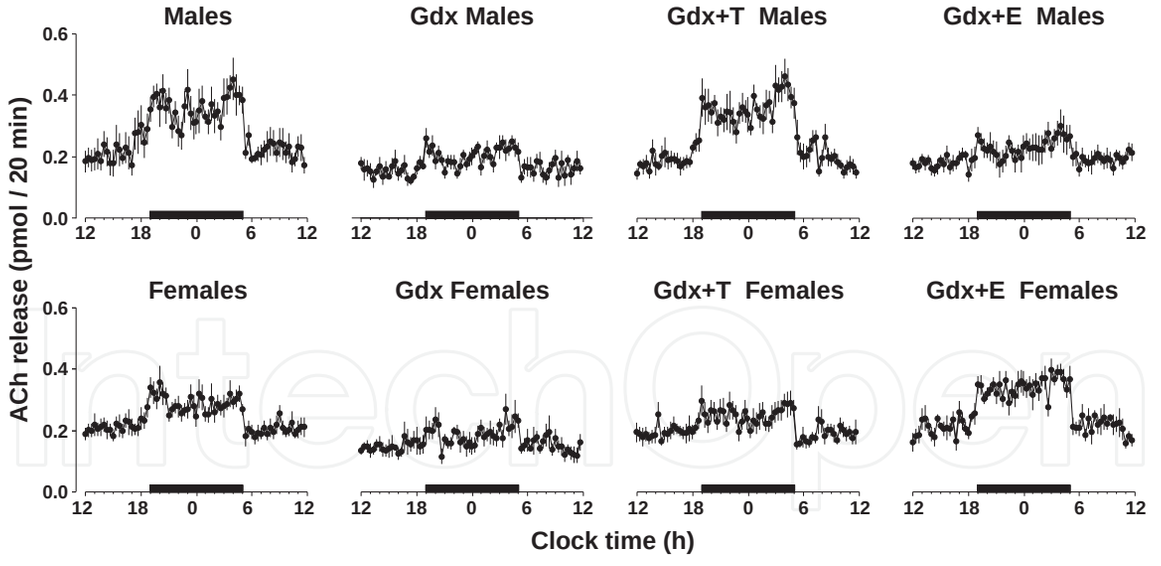

Figure 4. ACh release in the hippocampus is time-dependent, sex-specific, and hormone-dependent. Time-dependent ACh release may transmits the information such as time of day. Experiments were performed 2 weeks after gonadectomy or steroid replacement. Horizontal black bars indicate the dark phase. Gdx, gonadectomized. +T, testosterone-priming. +E, estradiol-priming. The number of animals was 6 to 8 in each group. 19h to 5h is the dark phase, shown as black bars on the x axes.(see Mitsushima et al., 2009)

Moreover, we found that after gonadectomy, the positive correlation between ACh release and locomotor activity levels was severely impaired, suggesting that hippocampal function

may not always be activated at low sex steroid levels (Mitsushima et al., 2009). This therefore suggests that learning impairment in gonadectomized rats (Gibbs and Pfaff, 1992; Daniel et al., 1997; Kritzer et al., 2001; Markowska et al., 2002; Luine et al., 2003) may be due to insufficient activation of hippocampus at the appropriate time. Because the replacement of sex-specific steroids restored the high positive correlation between ACh release and activity levels, the correlation appears to depend on the presence of sex steroids. These results suggest that circulating sex steroids strengthen the coupling between spontaneous behaviour and ACh release (Mitsushima et al., 2009).

7. Sexual differentiation produces the sex-specific activational effect

The activational effect of sex steroids was sex-specific (Figure 4). Testosterone replacement in gonadectomized female rats failed to increase ACh release to levels seen in gonadectomized testosterone-primed male rats. Similarly, estradiol replacement was unable to restore ACh release in gonadectomized male rats. Moreover, estradiol consistently increases N-methyl-D-aspartate receptor binding and spine density in the CA1 area of gonadectomized female rats, although the treatment fails to increase these same parameters in gonadectomized male rats (Romeo et al., 2005; Parducz et al., 2006). These results suggest that sex-specific steroids are important for maintaining hippocampal function. Based on our data, we hypothesized that the action of sex-specific steroids is due to neonatal sexual differentiation rather than the activational effects of sex steroids in adult rats. Moreover, in the latest study, we found that neonatal androgenization in females increased ACh release to resemble that of normal males without affecting spontaneous activity levels (Mitsushima et al., 2009). These results indicate an organizational effect on sex-specific ACh release in behaving rats, and support currently accepted theories of sexual differentiation.

Because testosterone can be aromatized to estradiol in the forebrain, neonatal sex steroids activate both estrogen and androgen receptors (McEwen, 1981). In our study, both testosterone and estradiol treatment in neonatal female pups masculinized ACh release profile in adults, suggesting an estrogen receptor-mediated masculinization of septo-hippocampal cholinergic systems (Mitsushima et al., 2009). These results are consistent with the previous finding that testosterone or estradiol treatment in neonatal female pups improves their adult spatial performance, whereas neonatal gonadectomy in male pups impairs the performance (Williams and Meck, 1991). In contrast, dihydrotestosterone treatment failed to masculinize the ACh release profile. Although dihydrotestosterone has been classically considered as a prototypical androgen receptor agonist, a metabolite of dihydrotestosterone, 3β-diol, has a higher affinity for estrogen receptor β (Lund et al., 2006). Therefore, dihydrotestosterone and its metabolites may stimulate both androgen receptor and estrogen receptor β, whereas estradiol stimulates estrogen receptor α and β. Considering the action of sex steroids and their metabolites, estrogen receptor α may mediate the organizational effect on the septo-hippocampal cholinergic system.

8. Interaction with environmental conditions

Various environmental conditions may interact with the activational effects of sex steroids. First, we reported an interaction between stress and sex steroids. Although sex steroids did not show activational effects on baseline levels of ACh release, sex steroids clearly activated the immobility stress-induced ACh release response. In addition, we found that the contributing sex hormone effect to maintain the ACh release response was sex-specific: testosterone enhanced the ACh release response in male rats, while estradiol maintained the response in females (Mitsushima et al., 2008). Second, we reported an interaction between the light/dark cycle and sex steroids. Although sex steroids slightly enhanced ACh release during the light phase, the activational effects were much stronger during the dark phase (Figure 4). Considering the fact that the time-dependent activational effect was also sex-specific and hormone-dependent, environmental conditions seem to have complicated interactions with sex steroids (Mitsushima et al., 2009).

Some other environmental effects may affect the basal forebrain cholinergic system. Environmental conditions, such as complex or restricted(Brown, 1968; Smith, 1972),enriched or impoverished (Greenough et al., 1972), social or isolated conditions (Hymovitch,1952; Juraska et al., 1984; Seymoure et al., 1996), seem to affect spatial learning ability in a sex-specific manner. For example, male rats exhibited superior performance in learning maze tests compared with female rats if they were housed socially (Einon, 1980). But if they were housed in isolation, female rats exhibited a performance superior to that of male rats (Einon, 1980). Although few studies were performed on the relationship between the sex-specific environmental effects and ACh release in the brain, we have reported that 4-day housing in a small cage attenuates the ACh release in the hippocampus in male rats (Mitsushima et al., 1998), but not in female rats (Masuda et al., 2005). Taken together, these results suggest that housing conditions contribute to the sex difference in ACh release and spatial learning ability.

Feeding conditions after weaning also affect spatial learning ability. If fed pelleted diet (i.e. standard laboratory diet), male rats show performance superior to that of female rats (Beatty, 1984; Williams and Meck, 1991). But when fed powdered diet, female rats, but not male rats, showed improved performance (Endo et al.,1994; Takase et al., 2005a). In our study, it was found that feedingwith powdered diet after weaning increased ACh release in the hippocampus in female rats, but not in male rats(Takase et al., 2005b). 24-HACh release in female rats fed powdered diet was as high as that in male rats fed either powdered or pelleted diet, showing no sex difference. Since feeding with powdered diet improved spatial learning ability in female rats (Endo et al., 1994), the increase in the ACh release in the hippocampus in female rats fed powdered diet may partly contribute to this effect. Our findings provide evidence that environmental conditions such as housing or feeding may play a role in sex-specific hippocampal function.

9. Aging and Alzheimer's disease

Activational effects of sex steroids are very important in humans, since circulating sex steroid levels decline with age. A reduction in ACh synthesis is known as a common feature of Alzheimer's disease (Coyle et al., 1983), afflicting more than 18 million people worldwide (Ferri et al., 2005; Mount and Downtown 2006). The disease is the most common form of dementia (Cummings 2004) and is frequently accompanied by insomnia, poor concentration, and day/night confusion (McCurry et al., 2004; Starkstein et al., 2005). The centrally active acetylcholinesterase inhibitor (donepezil) is effective in not only mild, but also moderate to severe cases (Petersen et al., 2005; Winblad et al., 2006), proving the importance of endogenous ACh in humans. In addition, women are twice as likely to develop the disease (Swaab and Hofman 1995), and estradiol seems to play a protective role (Zandi et al., 2002; Norbury et al., 2007). A recent study using single photon emission tomography showed that estrogen replacement therapy in healthy post-menopausal women increases muscarinic M_1/M_4 receptor binding in the hippocampus (Norbury et al., 2007). Conversely in men, testosterone but not estradiol seems to play a protective role (Moffat et al., 2004; Rosario et al., 2004) and testosterone supplementation clearly improved hippocampal-dependent learning deficits in men with Alzheimer's disease (Cherrier et al., 2005). These results suggest a sex-specific activational effect of gonadal steroids on the cholinergic system in humans. Thus, there are many similarities between the rat model and human studies, supporting the idea that gonadal steroid replacement therapy or an increase in bioavailability is beneficial when there is a subthreshold level of the hormone. Based on the neonatal sexual differentiation of the septo-hippocampal cholinergic system, we may have to search for sex-specific clinical strategies for Alzheimer's disease.

10. Conclusions

Gonadally intact male rats consistently show a greater ACh release in the hippocampus compared with diestrous or proestrous female rats. The activational effects of sex steroids are important for sex-specific ACh release in the hippocampus, since impaired ACh release in gonadectomized rats does not show sex-specific effects. Neonatal treatment with either testosterone or estradiol clearly increased ACh release in female rats, suggesting neonatal sex differentiation of septo-hippocampal cholinergic systems. Moreover, environmental effects on the basal forebrain cholinergic system seem to be sex-specific; housing in a small cage attenuated ACh release in male ratsonly, while feeding with powdered diet after sexual maturation increases ACh release in female ratsonly. These results indicate that: (i) sex-specific circulating sex steroids are necessary for sex-specific ACh release, (ii) neonatal activation of estrogen receptors is sufficient to mediate masculinization of the septo-hippocampal cholinergic system, and (iii) sex-specific effects of environmental conditions may suggest an interaction with the effect of sex hormones.

Understanding the importance of gonadal steroids and the sex-specific effects in cognitive disorders such as Alzheimer's disease is essential for real improvementsin therapy.

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