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The Role of Prolactin in the Regulation of Male Copulatory Behavior

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1. Introduction

In developed countries, the elderly population increases at an accelerated rate due to a decrease in the birth rate and the prolongation of life through medical development. Moreover, increases in the elderly population allow the prediction of an increase in hyperprolactinemia caused by aging. It is well known that hyperprolactinemia decreases libido and causes oligozoospermia [1]. On the other hand, hyperprolactinemia is caused by or associated with, a variety of pathogenic stages: pituitary adenoma, hypothalamic disorders, hypogonadism and hypothyroidism, and is detected in patients with infertility [2, 3], impotence and hypogonadism [4]. PRL is a polypeptide hormone that is synthesized and secreted from mammotropes in the anterior lobe of the pituitary gland [5]. Many studies have documented a critical role of PRL in the maintenance of lactation in women and female animals [6, 7] as well as in immunregulation in both, males and females [8], however, its role in sexual behavior is not entirely clear [9-16].

It has been also shown that DAerg agonists facilitate several aspects of copulatory behavior and *ex copula* genital responses [10]. DAerg neurons, locating in the medial preoptic area (MPOA), and the zona incerta (incertohypothalamic DAerg system) are the key centers in the stimulatory control of sexual functions [17-18]. (R)-salsolinol (SAL), a DA related and derived tetrahydroisoquinoline, has been recently identified as a strong candidate for being the endogenous PRL releasing factor (PRF) synthesized in both the hypothalamus and the neurointermediate lobe (NIL) of the pituitary gland. Analysis of SAL concentrations revealed parallel increase and decrease with the elevation and reduction of plasma PRL, respectively. SAL is sufficiently potent and selective *in vivo* to account for the massive discharge of PRL that occurs after physiological changes. At the same time, parallel with its DA depleting effect in sympathetically innervated peripheral organs, SAL can reduce testosterone secretion both *in vivo* and *in vitro* from Leydig cells [19-20]. Based upon all of

these data, the aim of our present studies was to confirm the suppressive effects of hyperprolactemia induced by grafting pituitary glands under the kidney capsule and to investigate the effect of a single injection of SAL on the elevation of plasma PRL and on sexual behavior in male rats.

Sexually experienced male rats of the Wistar-Imamichi strain (Imamichi Institute for Animal Reproduction, Tsuchiura, Japan), approximately 10 weeks old at the start of the experiments, were used. The animals were kept in a room with a temperature of 22-26 Celsius and subjected to a light-schedule of 14 hrs light and 10 hrs darkness (lights off at 19:00). They were provided with pellet diet CRF-1 (Charles River Laboratories Japan, Atsugi, Japan) and water ad libitum. Stimulus females of the same strain were rendered sexually receptive by treatment with estradiol benzoate (10 μ g/0.1 ml sesame oil, Sigma Chemical Co. Ltd., St. Louis, USA) 48 hrs prior to, and progesterone (500 μ g/0.1 ml sesame oil, Sigma Chemical Co. Ltd., St. Louis, USA) 4 hrs prior to exposure to males.

One group of experimental animals were anesthetized with Nembutal (40 mg/kg, i.p.) and implanted one and two whole pituitaries from male donors with the same age in the same strain under the left kidney capsule [21]. Rats having 1 or 2 pituitary grafts were sacrificed by decapitation between 19:30 and 20:30 in a week after the test. It was carried out in 30 seconds after taking animals out from their cages [22-23].

In a separate group of animals, intravenous (i.v.) cannula have been inserted into the jugular vein of male Sprague-Dawley rats for injection of SAL, and being able to take blood samples. Saline or SAL (4 mg/kg body weight i.v.) have been injected to the animals prior to expose them to females being in estrus.

Copulatory behavior test have been conducted four weeks after the surgery. After a male rat was placed in the semi-circular observation cage (radius 40, height 50 cm) faced with Plexiglass under low-level red-light illumination for a few minutes, a sexually receptive female was introduced to its cage. Tests lasted 60 min from the introduction of the female. Behavioral testing was conducted between 19:30 and 20:30. The behavior categories scored included the following [24]. *Mounting frequency* (MF): number of mounts without intromission preceding ejaculation. *Intromission frequency* (IF): number of mounts with intromission preceding ejaculation. *Ejaculation frequency* (EF): number of ejaculations during 60 min. *Mount latency* (ML): time from the presentation of the female to the male's first mount. *Intromission latency* (IL): time from the presentation of the male's first intromission. *Ejaculation latency* (EL): latency from the first intromission until ejaculation. *Post-ejaculatory interval* (PEI): latency from ejaculation to the next intromission.

Blood collected and centrifuged at 3,000 g for 15 minutes for the analysis of serum hormone. The serum was stored at -80 Celsius until analyzed by RIA for determination of serum PRL, LH and FSH. Serum concentrations of PRL, LH and FSH were measured by RIA using the method of Furudate et al. [25] with reagents provided from NIADDK. The standard references used were, rPRL-RP-3 for PRL, rLH-RP-2 for LH and rFSH-RP-2 for FSH. The intra- and inter-assay coefficients of variation were 9.6 and 15.9 for PRL, 3.5 and 5.3 for LH, and 5.3 and 9.8 for FSH, respectively. Testosterone levels were also measured by direct RIA.

All data are presented as mean \pm SEs. The results from the copulatory behavior testing were analyzed using Fisher's exact probability test and the Mann-Whitney U test and the data for hormone levels and organs weights were analyzed by Duncan's multiple t-test.

2. Effect of pituitary transplants induced hyperprolactinaemia on copulatory behavior

The results of serum hormone levels in two pituitaries grafted and sham animals are shown in Table 1. Prolactin (PRL) concentration in rats having two pituitary grafts was significantly higher than sham operated animals ($p < 0.05$). There were no significant differences in the serum levels of luteinizing hormone (LH), folliclestimulating hormone (FSH) and testosterone between the same groups of animals.

Group	LH (ng/ml)	FSH (μ g/ml)	Prolactin (ng/ml)	Testosterone (ng/ml)
Graft	1.3 \pm 0.16	65.3 \pm 13.60	31.1 \pm 3.40 ^a	2.1 \pm 0.29
Sham	1.3 \pm 0.20	97.4 \pm 9.84	7.2 \pm 1.51 ^b	2.6 \pm 0.24

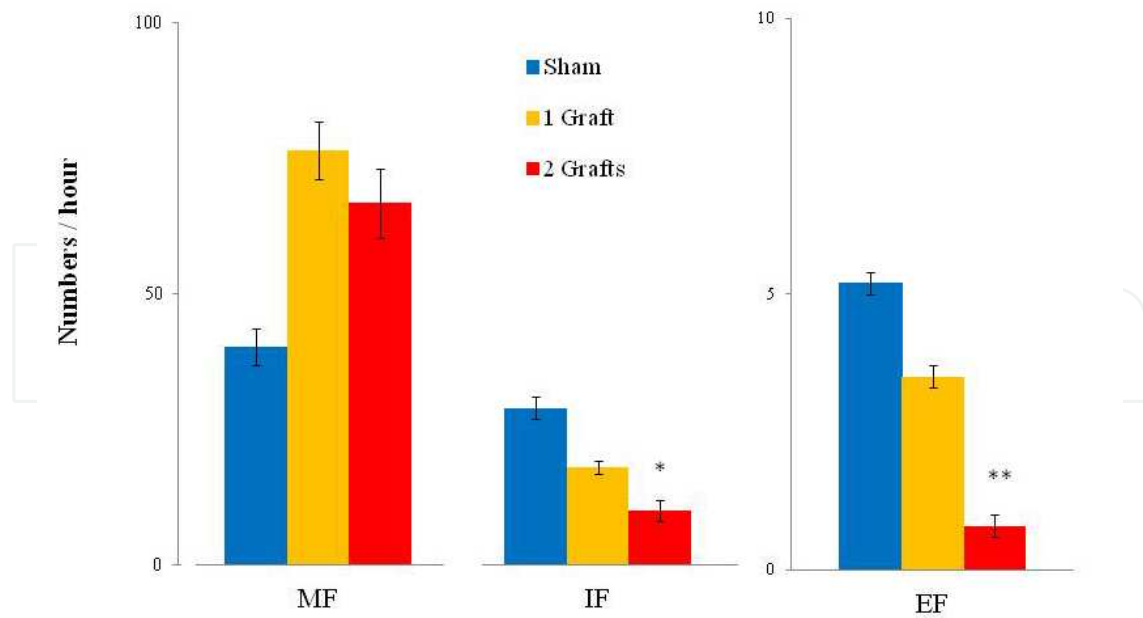
All data represent mean \pm S.E.

* $p < 0.05$ a vs. b

Table 1. Serum hormone levels in grafted male rats

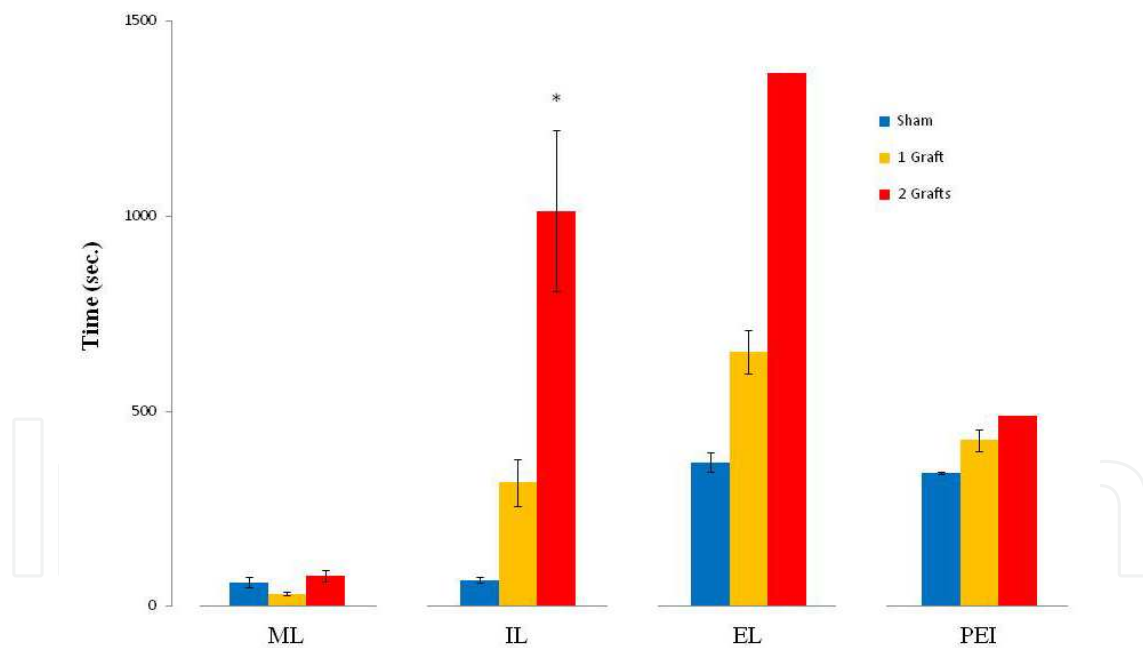
As it is shown on Fig. 1, the mean number of mount in rats having one-, two grafted pituitaries and non was 76.5 ± 5.35 , 66.8 ± 6.37 and 40.2 ± 3.43 , respectively. The mount frequency (MF) showed a tendency to be higher in grafted, compared with sham-operated animals. The mean frequency of intromission (IF) was lower for one (18.0 ± 1.27) and two pituitaries grafted males (10.0 ± 2.00), compared to sham-operated controls (29.0 ± 2.00). There were significant differences in IF between two pituitaries grafted and sham-operated males ($p < 0.05$). Ejaculation could be detected in all one-pituitary grafted and sham-operated males, while did not in 4 out of 6 two-pituitaries grafted males. The mean ejaculation frequency (EF) of one, two pituitaries grafted and sham males was 3.5 ± 0.33 , 0.8 ± 0.20 and 5.2 ± 0.20 , respectively. The EF of two pituitaries grafted males is significantly lower than sham males ($P < 0.01$).

As shown on Fig. 2, having two pituitary grafts resulted in a significant prolongation in the mean latency of intromission, compared with sham-operated animals ($1,014.4 \pm 206.12$ versus 67.8 ± 7.72 sec, $p < 0.05$). The mean latency to the first ejaculation showed a tendency to extend in animals having one (652.1 ± 56.06 sec), two ($1,367.5$ sec) pituitary grafts, compared with sham-operated males (369.7 ± 25.28 sec). The post-ejaculatory interval (PEI) tended to extend in animals having one (425.7 ± 27.40 sec) or two (487.5 sec) pituitary grafts, compared with sham-operated animals (341.7 ± 3.27 sec).



MF: Mount frequency. IF: Intromission frequency. EF: Ejaculation frequency. *p<0.05:2 Grafts vs. Sham; **p<0.01:2 Grafts vs Sham

Figure 1. Copulatory behavior in pituitary-grafted male rats.



MF: Mount frequency. IF: Intromission frequency. EF: Ejaculation frequency. PEI: Post-ejaculatory interval *p<0.052 Grafts vs. Sham;

Figure 2. Copulatory behavior in pituitary-grafted male rats

3. Effect of SAL on copulatory behavior

Plasma PRL concentrations of control and SAL groups at 15 min before exposure to females were 7.3 ± 2.0 and 8.0 ± 1.5 ng/ml, respectively. Moreover, plasma PRL concentrations in

males immediately after exposure to the females were 7.4 ± 1.2 and 68.0 ± 5.9 ng/ml, respectively. All (8 out of 8) of the control animals ejaculated in the presence of the female, whereas only 33% (2 out of 6) of the SAL group ejaculated. An increasing tendency for mount latency and intromission latency as well as a decreasing tendency for intromission frequency has been observed in the SAL injected group compared to the controls.

Group	Basal (ng/ml)	After Exposure (ng/ml)	Ejaculation Frequency
Control	7.3 ± 2.0	7.4 ± 1.2^a	100%
SAL	8.0 ± 1.5	68 ± 5.9^b	33%

All data represent mean \pm S.E.
* $p < 0.05$ a vs. b

Table 2. Effect of SAL on Plasma PRL levels and copulatory behaviour

4. Discussion

In male subjects, parallel with the age related testosterone depletion, there is a gradual increase of plasma PRL, generally referred as hyperprolactinemia, which is strictly related with a decrease of libido, erectile dysfunctions and oligozoospermia. It is an important issue in humans, because the proportion of elderly generation increases in developed countries, therefore, they also face to the same problems. Our data confirm previous results that only a mild but sustained elevation of PRL secretion is enough for inhibiting copulatory behavior. However, the exact neuronal and/or endocrine background of these age-related changes is not completely known. Our results underline the relationships between DA and its metabolite, SAL, in the regulation of sexual behavior and put a new player into the focus of this field. SAL cannot pass the blood-brain barrier, therefore, it likely affects copulatory behavior out of this barrier. In theory, anterior lobe of the pituitary gland may be one of the sites. In spite of the well documented PRL releasing activity of SAL *in vivo*, it has been also shown that SAL does not have a significant PRL releasing activity *in vitro*. Therefore, it can be hypothesized that SAL induces an elevation of plasma PRL as well as inhibition of the copulatory behavior through indirect pathways, which can communicate with each other. Short time elevation of plasma PRL that can be detected after SAL treatment just before copulation may be enough to inhibit copulatory behavior, but it needs further investigations.

Interestingly enough, SAL is also supposed to be formed after taking alcohol, and negative effect of alcohol on sexual behavior is also well known. Based on all of these, if we can learn more about the role of SAL in the regulation of sexual behavior, it shall be advantageous not only for basic research but it may give a chance to find the way to use agonists or antagonists of this molecule for using them in the medical or clinical fields. Although some progress has been made in identifying neurotransmitter-receptor effects on behavioral components of the copulatory behavior, but it is rather complex, and no drug has been found yet to affect only a single component.

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