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Involvement of a Direct Neural Mechanism in the Control of Gonadal Functions

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Much time has been devoted to study of the hypothalamo–hypophyseal–gonadal axis. However, there is now evidence of a complementary control mechanism for the gonads, namely a pituitary-independent, direct neural link that exists between the central nervous system and the gonads. We investigated whether mediobasal temporal lobe structures could control gonadal functions by a purely neural mechanism or whether they acted through the classical hypothalamo–hypophyseal system. Right- or left-sided deafferentation of the temporal lobe was combined with right- or left-sided hemicastration in adult and prepubertal male and female rats. In adult females right-sided deafferentation, regardless of the side of hemiovariectomy significantly reduced the extent of compensatory ovarian hypertrophy. Similar lesions on the left side did not interfere with the usual compensatory ovarian growth. This difference in compensatory hypertrophy between right- and left-sided lesioned rats was observed even in the face of a significant drop in serum LH concentrations in both groups. In pre- and postpubertal females temporal lobe lesion in either side was unable to alter compensatory hypertrophy or serum LH or progesterone concentrations. In adult male rats only left-sided deafferentation combined with left orchidectomy resulted in decreased T production, while in prepubertal male rats, only right-sided brain surgery plus left orchidectomy resulted in a significant decrease in basal testosterone secretion of the remaining testis. These findings indicate that mediobasal temporolimbic structures are involved in the neural control of gonadal functions. It appears that this lateralized mechanism is age- and sex-dependent.

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INTRODUCTION

In recent years the evidence has been strengthening in favor of the existence of a direct neural link between the gonads and the central nervous system. This is in addition to the classical hypothalamo–hypophyseal–gonadal neuroendocrine regulatory system, and this direct link might provide a complementary mechanism by which the brain could control reproductive functions.

Early studies indicated that following unilateral ovariectomy the protein-synthesizing activity of the hypothalamic arcuate nucleus increased on the side contralateral to hemicastration and no alteration on the ipsilateral side [1]. Hemiovariectomy also induced unilateral changes in the luteinizing hormone-releasing hormone (LHRH) content of the medio-basal hypothalamus [2]. Unexpectedly, these studies also revealed that in intact control rats the LHRH content of the two sides of the hypothalamus differed significantly with higher concentrations of LHRH found on the right versus the left side. Furthermore, hypothalamic lesions on the right side have been reported to prevent the development of compensatory ovarian hypertrophy in adult rats with ipsilateral ovariectomy [3], while in prepubertal rats deafferentation on the left side of the hypothalamus was effective in reducing the extent of compensatory ovarian growth [4]. Fukuda *et al.* [5] have also observed that in adult rats right-sided lesion of the anterior hypothalamus suppressed compensatory ovarian hypertrophy regardless of the side of ovariectomy. All these findings suggest that in addition to the neuroendocrine–endocrine regulatory mechanism, a direct neural link between the central nervous system and the ovary could also contribute to the control of ovarian functions. This view is also supported by the observation that in hypophysectomized and hemiovariectomized rats the atrophy of the remaining gland

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is less severe than in rats that underwent solely hypophysectomy [6]. Furthermore, it was reported that in hypophysectomized animals unilateral electrical stimulation of certain cerebral structures could induce monolateral changes in ovarian steroid input [7]. These data are consistent with the postulate that a pituitary-independent mechanism is involved in the control of female reproductive processes.

In males, the existence of a direct neural mechanism in the control of gonadal functions has been less extensively studied. The available data indicate that such a regulatory mechanism might also work in the control of testicular functions. In adult rats unilateral orchidectomy was associated with a significant rise in the LHRH content of the hypothalamus ipsilateral to hemicastration [8]. In addition, unilateral hypothalamic lesion was reported to interfere with the hemiorchidectomy-induced FSH rise if right-sided brain surgery was combined with right-sided orchidectomy [9]. In adult rats with two testes, right-sided vagotomy resulted in a significant increase in serum LH concentration while a similar intervention on the left side had no effect on gonadotrophic hormone levels [10].

The involvement of temporolimbic structures, including the amygdala, in the control of gonadal functions is well documented. In adult female rats bilateral lesioning of the cortical amygdaloid nucleus prevented the development of compensatory ovarian hypertrophy [11, 12], however, similar surgery in prepubertal female rats had no effect on compensatory ovarian growth [13]. Similarly, in adult male rats bilateral amygdalectomy resulted in severe degeneration of the testes [14]. Since bilateral lesions were performed in these studies, the inhibitory effect of lesions of the amygdaloid on gonadal functions was interpreted as a suppressive action of the surgery on the hypothalamo–hypophyseal GnRH–LH/FSH system, and not a direct effect on the gonads.

Therefore, we investigated whether right- or left-sided deafferentation of the medial basal portion of the temporal lobe in female rats affected serum gonadotropin levels and compensatory ovarian hypertrophy. In prepubertal animals the timing of puberty was also measured [15]. Similar right- or left-sided temporal lobe deafferentations were also performed in adult and prepubertal hemicastrated male rats, and in the remaining testis testosterone secretion *in vitro* was determined.

INVOLVEMENT OF TEMPORAL LOBE STRUCTURES IN THE NEURAL CONTROL OF THE OVARY

Right- or left-sided deafferentation of the medial basal portion of the temporal lobe (including the corticomedial amygdaloid nucleus) was performed with a bayonet-shaped knife [16]. Immediately after brain surgery the right or the left ovary was removed. Animals were sacrificed 9 days postsurgery.

Adult females

In each experimental group hemiovariectomy resulted in a significant weight increase of the remaining gonad. However, in animals with right-sided deafferentation in the temporal lobe the rate of compensatory ovarian hypertrophy was significantly lower than in rats that underwent solely hemiovariectomy. The suppressive effect of the lesion was independent on the side of ovariectomy. In contrast, left-sided brain surgery did not interfere with the usual compensatory ovarian growth. These data indicate that right- but not the left-sided temporal lobe structures are involved in

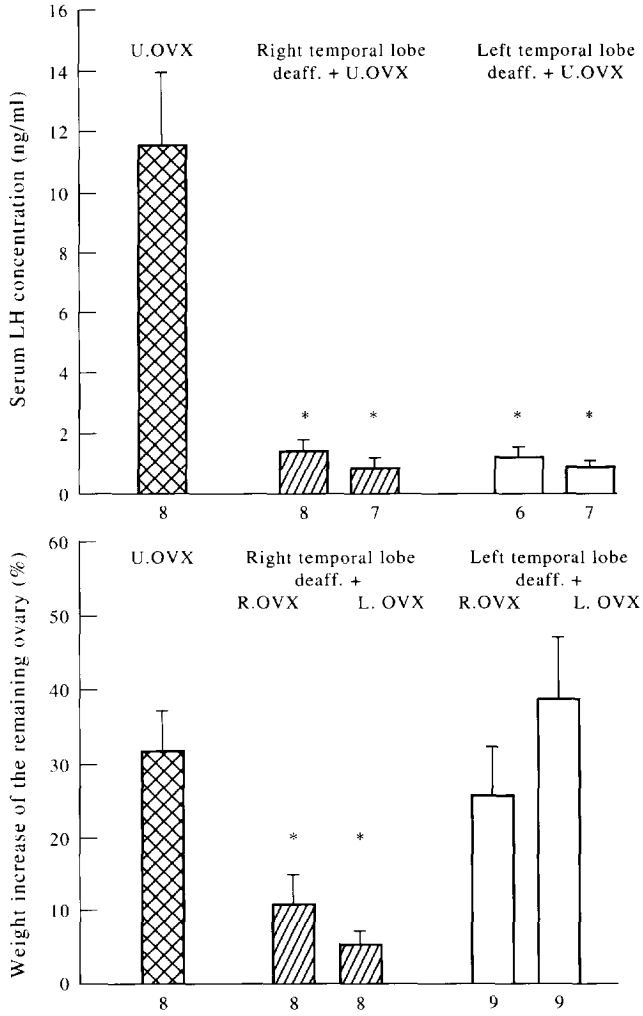

Fig. 1. The effect of right- or left-sided mediobasal deafferentation (deaff.) of the temporal lobe on compensatory ovarian hypertrophy (lower panel) and on serum LH concentration (upper panel) in adult female rats 9 days postsurgery. The data are mean ± SEM. U.OVX, unilateral ovariectomy; R.OVX, right ovariectomy; L.OVX, left ovariectomy. The asterisk indicates significant difference from the hemiovariectomized, non-deafferentated group.

the control of the development of compensatory ovarian hypertrophy (Fig. 1, lower panel).

In hemiovariectomized rats both right- and left-sided deafferentation in the temporal lobe resulted in a significant drop in serum LH concentration (Fig. 1, upper panel). Serum FSH levels showed no alterations in any experimental group. The lack of correlation between the changes in compensatory ovarian hypertrophy and serum gonadotropin hormone concentrations suggests that the right-sided lesion in the temporal lobe exerts a suppressive effect on compensatory ovarian growth by a pituitary-independent mechanism.

Postpubertal females

Right- or left-sided temporal lobe deafferentation and hemiovariectomy were performed shortly after vaginal opening in female rats. The rate of compensatory ovarian hypertrophy following right-sided deafferentation was similar to that observed in rats that underwent hemiovariectomy but not brain surgery. Following left-sided deafferentation, compensatory ovarian growth was slightly, but not significantly, reduced compared to either hemicastrates or hemicastrated plus right-sided lesioned animals (Fig. 2, lower panel).

Serum progesterone concentrations decreased slightly following hemicastration. In animals with right- and left-sided deafferentation serum progesterone levels were slightly higher than in hemicastrates with no brain surgery, but the changes in progesterone concentrations were not significant (Fig. 2, upper panel).

Prepubertal females

In 27-day-old rats, right- or left-sided deafferentation and/or right- or left-sided ovariectomy were performed. Animals were sacrificed 28 days postsurgery.

Ovarian weights and serum LH and FSH concentrations were not different following sham brain surgery or right or left deafferentation in the temporal lobe in animals with intact ovaries. The day of vaginal opening of sham operated rats or animals with right- or left-sided deafferentation did not differ from that of intact controls.

The day of vaginal opening for rats with sham lesions on the left side was slightly, but not significantly delayed compared to control animals, while in animals with left-sided deafferentation it was slightly advanced. Therefore, a slight, but significant difference in timing of puberty could be observed between animals with sham surgery on the left side and left-sided deafferentation (Fig. 3).

In hemicastrates the rate of compensatory ovarian hypertrophy and serum FSH levels were similar between groups (data not shown). The timing of puberty and serum LH concentrations following sham brain surgery or right- and left-sided temporal lobe lesion

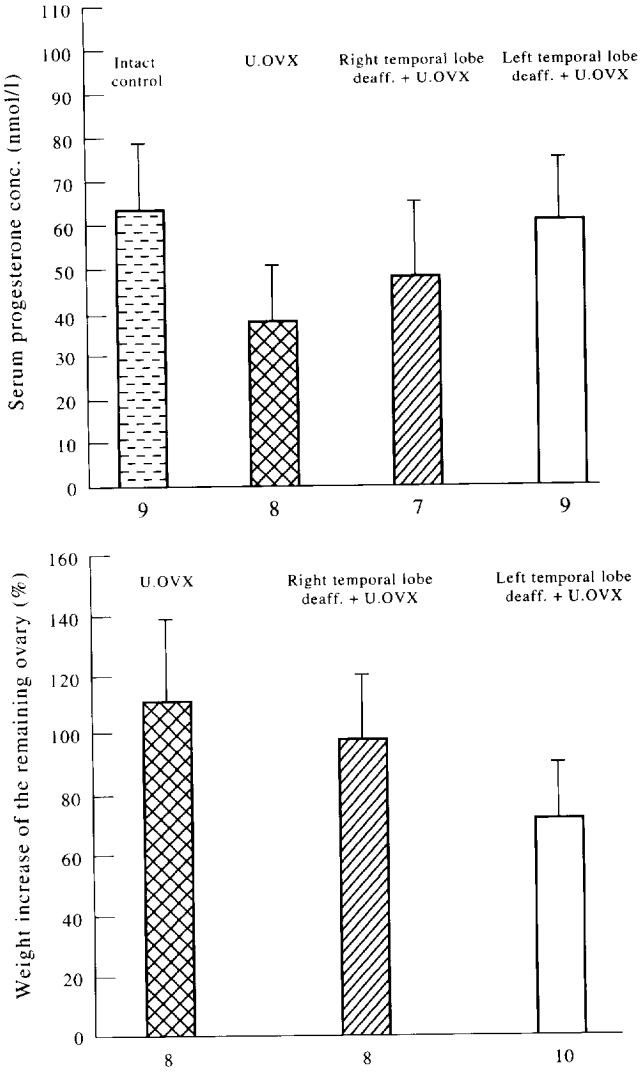

Fig. 2. The effect of right- or left-sided mediobasal deafferentation (deaff.) of the temporal lobe on compensatory ovarian hypertrophy (lower panel) and on serum progesterone concentration (upper panel) in rats deafferented and hemiovariectomized shortly after vaginal opening, and sacrificed 9 days postsurgery. The data are mean ± SEM. U.OVX, unilateral ovariectomy.

were altered only by one treatment. Right-sided deafferentation combined with left-sided ovariectomy resulted in advanced vaginal opening and a significant elevation in serum LH levels (Fig. 4).

INVOLVEMENT OF TEMPORAL LOBE STRUCTURES IN THE NEURAL CONTROL OF THE TESTIS

In adult and 30-day-old rats right- or left-sided deafferentation of a small portion of the medial basal part of the temporal lobe was carried out. Brain surgery was followed by right- or left-sided hemiorchidectomy. Animals were sacrificed 7 days following interventions. Immediately after sacrifice the testes were removed, incubated, and testosterone production was determined.

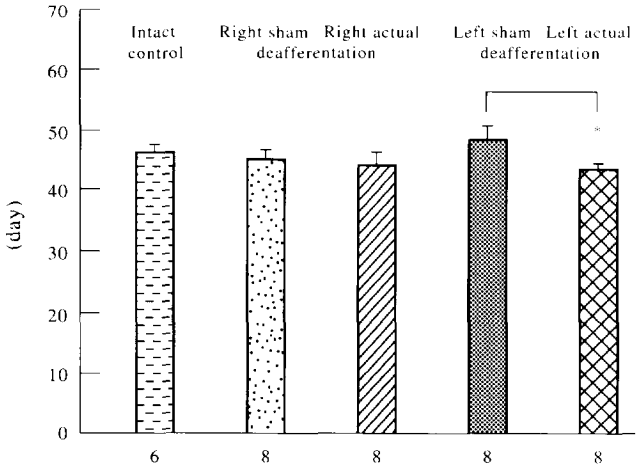

Fig. 3. The effect of right- or left-sided sham or actual mediobasal deafferentation of the temporal lobe on the time of vaginal opening in intact animals. Animals were deafferented on Day 27 of age, and sacrificed 28 days postsurgery. Data are mean ± SEM. The asterisk indicates significant difference from the left-sided sham deafferented group.

Adult males

Following right- or left-sided deafferentation, basal testosterone production of the remaining testes was unchanged compared to testes from animals following hemicastration only. The one exception to this was the case when left-sided deafferentation was combined with left orchidectomy. In these rats basal testosterone secretion was significantly lower than that in left orchidectomized rats with no brain surgery or in animals with left-sided deafferentation plus right-sided orchidectomy. This observation indicates that in adults testicular steroidogenesis is controlled by left-sided temporal lobe structures. Furthermore, besides the functional laterality of the temporal lobe, testes also exhibit an asymmetry, at least, as far as steroidogenesis is concerned (Fig. 5).

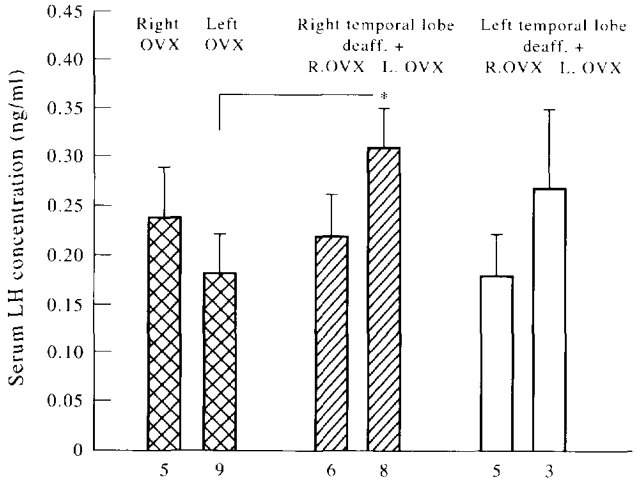

Fig. 4. The effect of right- or left-sided mediobasal deafferentation of the temporal lobe on serum LH concentrations in prepubertal hemiovariectomized animals. Animals were operated on Day 28 of age, and sacrificed 28 days postsurgery. Data are mean ± SEM. R, right; L, left; OVX, ovariectomy. The asterisk indicates significant difference from the group that underwent solely left ovariectomy.

Prepubertal males

In contrast to the results obtained in adults, in prepubertal rats steroidogenesis was suppressed in deafferented plus left hemicastrated rats if brain surgery was performed on the right side (Fig. 6). It is of note that neither in adult nor in prepubertal rats no change in serum LH concentrations could be observed.

DISCUSSION

The present data indicate that unilateral lesions of temporolimbic structures can modify gonadal functions. Since suppressive effects of unilateral deafferentation on gonadal parameters were not accompanied with parallel decreases in serum gonadotropin hormone concentrations, the mechanism by which the affected structures exert their action on the gonads is a neural, pituitary-independent one. Our observations demonstrate that the effectiveness of the unilateral lesion depended on multiple factors, such as the side of brain intervention, and the sex and age of animals (as well as on the parameter studied). This suggests that the temporolimbic neural control over gonadal functions is lateralized, and the dominance is sex- and age-dependent.

These observations are in accordance with clinical data. Reproductive endocrine disorders are more common among men and women with temporal lobe epilepsy than in the general population. Partial seizures of temporal lobe origin are more frequently associated with reproductive and sexual dysfunction than general or focal motor seizure disorders [17]. In women with right-sided epileptiform discharges of temporal lobe origin, the occurrence of hypogonadotropic hypogonadism is significantly greater than in the general female population or in the case of left-sided partial epilepsy. In contrast, there is a strong predominance of left-sided seizures with polycystic ovarian syndrome [18]. In male patients, partial seizures of temporal lobe origin are often associated with hypogonadotropic hypogonadism, hyperprolactinemia or hypergonadotropic hypogonadism, but no positive correlation was found between the pattern of endocrine disorder and the lateralization of epileptiform discharges. The exception being the cases in which abnormally high or low prolactin secretion occurred; these individuals had right-sided paroxysmal discharges [19].

The neural route by which the medial basal portion of the temporal lobe could regulate gonadal function is not entirely known. However, the amygdala has direct efferent connections to the dorsomedial and lateral regions of the hypothalamus [20] and the dorsal motor nucleus of the vagus [21]. The dorsal motor nucleus of the vagus regulates sympathetic response via direct connections with the intermediolateral cell column of

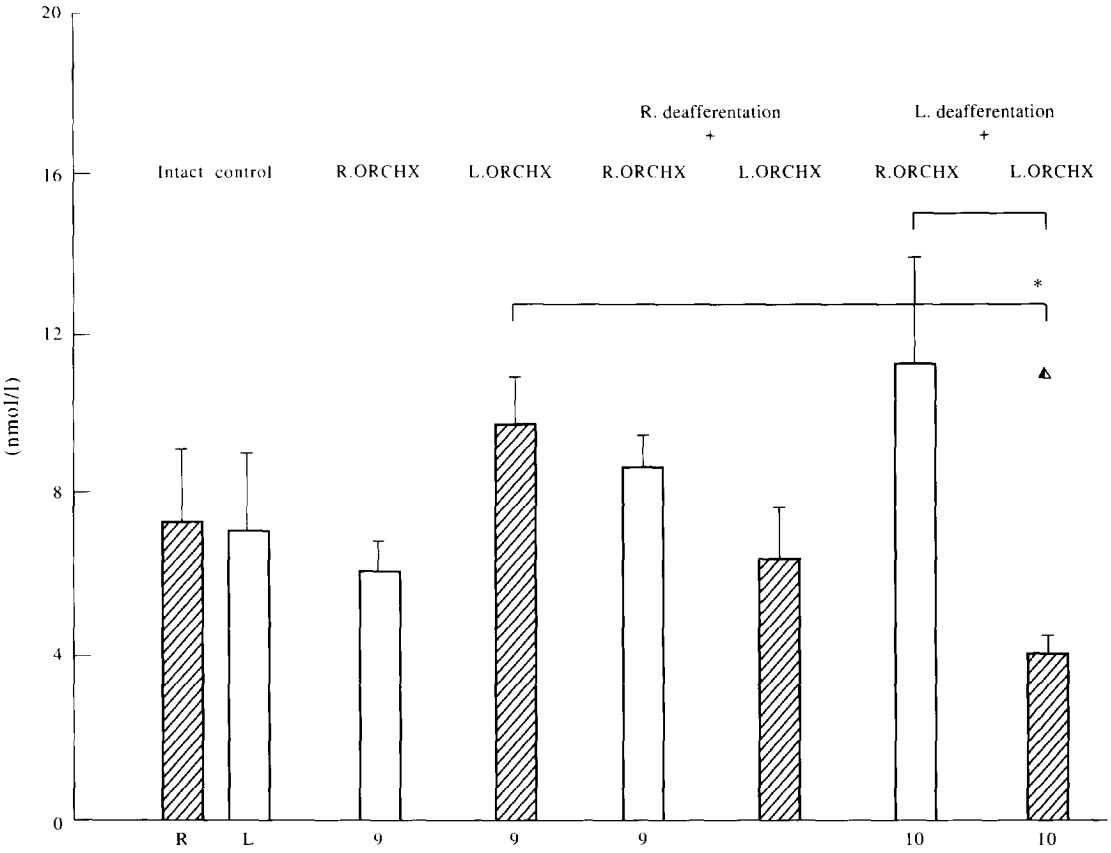

Fig. 5. The effect of right- or left-sided mediobasal deafferentation of the temporal lobe on basal testosterone secretion *in vitro* in hemiorchidectomized adult rats. Animals were sacrified 7 days postsurgery. The data are mean ± SEM. R, right; L, left; ORCHX, orchidectomy. The asterisk indicates significant difference from the left orchidectomized and from the left deafferented plus right orchidectomized groups.

the spinal cord [20]. Furthermore, vagal fibers from the gonads terminate in the nucleus of the solitary tract that has extensive reciprocal connections with the hypothalamus, the amygdala and other structures involved in the regulation of reproductive processes [22].

The mechanisms that determine the pattern of the above described functional asymmetry in the temporal lobe are unknown. Nevertheless, morphological [23] and biochemical [24] asymmetries of the temporal lobe are well documented. Evidence has also been presented that biochemical asymmetry is present in the hypothalamus. Besides the asymmetrical distribution of hypothalamic LHRH in female rats [2], acetyl-cholinesterase activity has been reported to be significantly higher on the right than on the left side [25]. In addition, implantation of atropine on the left side of the hypothalamus on day 2 of diestrus blocked ovulation, while implantation on the right side did not interfere with ovulation. Furthermore, data also indicate that the hypothalamic dominance is shifted to the opposite side in estrus [26]. Lesion studies have also revealed functional asymmetry of hypothalamic structures in the control of ovarian functions [3, 4, 5]. These observations are consistent with our findings on the existence of a lateralized control mechanism in the temporal lobe, however, it remains to be determined whether there is a causal relationship between hypothalamic and temporal lobe dominance.

It is of note that in adult female rats right-sided lesions in the temporal lobe reduced the rate of compensatory ovarian hypertrophy regardless of the side of hemiovariectomy, and the effect was not present in pre- or postpubertal animals. In contrast, in males, the development of the suppressive effect of deafferentation depended not only on the side of brain surgery, but on the age of the animals and the side of hemicastration (alternative, the side of the remaining testis).

As far as testicular asymmetry is concerned, Chang *et al.* [27] have reported that in humans the right testis is heavier than the left. In humans cryptorchism and varicocele are more frequently found on the left side [28]. Similarly, greater vulnerability of the left testis has been observed in hemivasectomized neonatal [29] and adult rats [30]. The present findings also indicate that the two testes can respond different to the same intervention.

The observation that in adult rats left-sided, while in prepubertals right-sided, temporal lobe surgery could suppress steroidogenesis suggests that during ontogenesis dominance can shift from one side to the other. Consistent with this observation Ross *et al.* [31] have demonstrated that both left-to-right and right-to-left

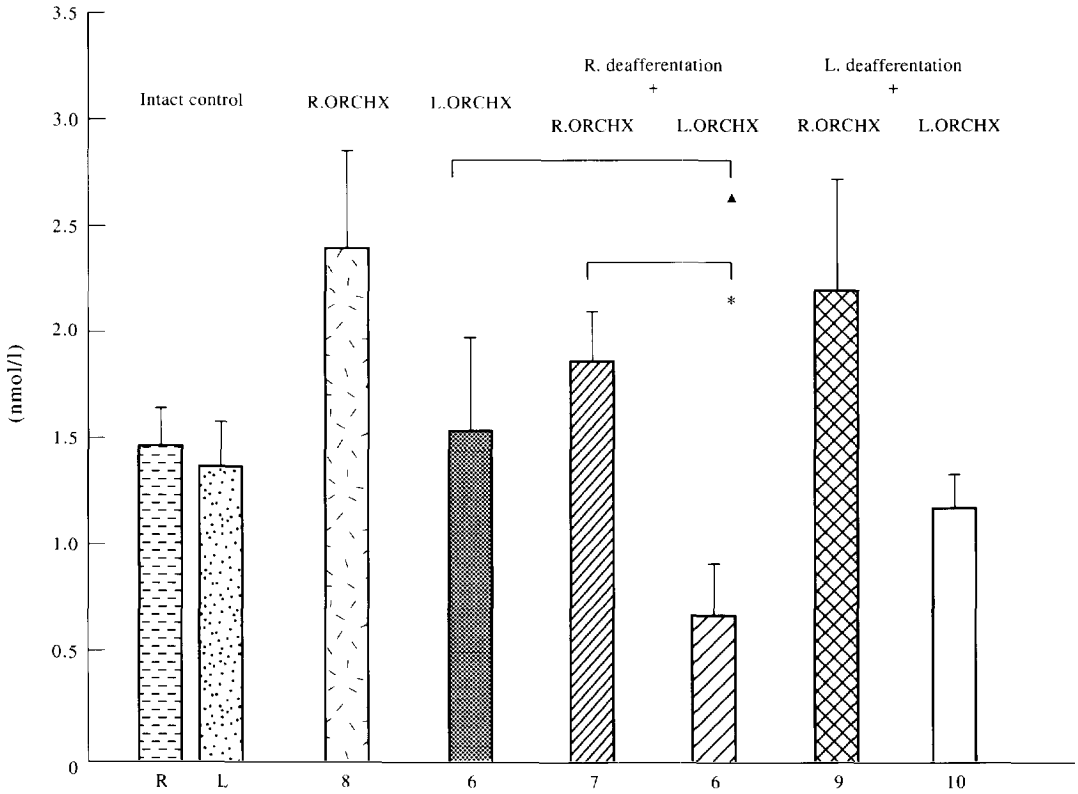

Fig. 6. The effect of right- or left-sided mediobasal deafferentation of the temporal lobe on basal testosterone secretion *in vitro* in hemiorchidectomized prepubertal rats. Animals were operated on Day 30 of age, and sacrified 7 days postsurgery. The data are mean ± SEM. R, right; L, left; ORCHX, orchidectomy. The asterisk indicates significant difference from the left orchidectomized and from the right deafferented plus right orchidectomized groups.

maturational gradients exist in different brain areas during the postnatal developmental period in the rat. Such gradients are structure and age dependent.

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