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INTERACTIONS BETWEEN OVARIAN STEROIDS OR PROGESTAGENS AND LH RELEASE

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SUMMARY

There is no doubt today that preovulatory LH surge is related to previous oestrogen secretion in domestic animals. An increase in plasma 17β-oestradiol precedes LH surge in natural conditions, but the surge can be induced by oestrogen treatment in the anestrous or castrated ewe. Thus, a 50 μg injection of oestradiol benzoate induces, in 90 p. 100 of castrated females, a LH peak of the same magnitude but of longer duration (16.30 hours *vs* 10.30 hours, $P < 0.01$) than observed during the estrous cycle. Conversely, although progesterone probably has a positive indirect effect on preovulatory surge, it appears to act mainly as an inhibitor under experimental conditions. No castrated ewes display a LH peak after one progesterone injection (25 mg) or a series of injections ; in all cases, further progesterone treatment inhibits the positive effect of 17β-oestradiol (4 to 8 females per group).

Little is known about the effect of steroids at the hypothalamic level, although it is thought that the positive feedback effect of oestrogens and the negative feedback effect of progesterone are exerted at this site. The influence of oestrogen is suggested by a 50 p. 100 decrease in LRF activity at the time of LH surge, interpreted as a LRF release. A progesterone effect at the hypothalamic level may be deduced from studies in which progestagens induce a decrease in LRF activity of lactating ewes in the absence of any LH surge. This decrease reaches 15 and 32 p. 100 of the control values in females treated with 20 or 40 mg, respectively, of fluorogestone acetate.

A more recent demonstration of the interplay between steroids and hypothalamo-pituitary activity is the variation of pituitary responsiveness to LRF during the estrous cycle. In ewes, an intravenous LRF injection induces LH release, which varies according to the stage of the estrous cycle. Mean LH response after a 25 μg LRF injection is 57, 23, 18 or 146 ng/ml/1 hour when LRF is given on day 4, 8, 12 or 16, respectively, of the estrous cycle. This LH response is correlated with the oestrogen/progesterone plasma ratio ($r = + 0.97$, $P < 0.05$) which appears to regulate LRF effect at the pituitary level.

A relationship between steroids and preovulatory LH surge was suggested as early as 1934 ; HOHLWEG showed that oestrogen injection induced ovulation in rats. This « Hohlweg effect » was later found again in the ewe (HAMMOND, 1945),

but 25 years more were to elapse before discovery of the physiological bases of these facts in domestic animals. On the other hand, after a period of latency, as soon as circulating hormones could be measured, the problem of steroid-LH release interaction was widely studied. From a fundamental point of view, the relationship between hypothalamus, pituitary and gonads appeared more complex than the simple feed-back mechanism first conceived ; on the other hand in medical or zootechnical fields, the control of this LH release appeared to be of utmost importance, namely because progestagens were used to regulate sexual cycles.

Determination of hormone plasma levels, delimitation of the respective roles of oestrogens and progesterone, and the effects of the latter on the hypothalamus and the pituitary have been the main lines of research in endocrinological studies of the periovulatory period.

I. — PREOVULATORY LH RELEASE AND CIRCULATING STEROIDS DURING THE ESTRUS PERIOD

1. — *Steroid and LH variations before ovulation in the ewe*

Hormonal variations occurring at the time of estrus have been studied in greater detail in the ewe than in other domestic animals. At the end of the estrous cycle, three major variations occur involving progestins, oestrogens and pituitary hormones.

Thus, progesterone measured in the ovarian vein from the ovary bearing the corpus luteum decreases by 100 fold (from 1 000 to 10 ng/ml) between 48 and 24 hours before estrus when luteolysis occurs (BJERSING *et al.*, 1972 ; MOORE *et al.*, 1969). On the contrary, oestrogens (oestradiol-17β) increase from some tens of pg/ml to more than 1 ng/ml before estrus (BJERSING *et al.*, 1972 ; MOORE *et al.*, 1969 ; SCARAMUZZI *et al.*, 1970 ; COX *et al.*, 1971), then decline rapidly between 6 and 16 hours after onset of estrus (MOORE *et al.*, 1969). Similar variations are observed in the peripheral blood, but they are smaller. Progesterone varies from 2-3 ng/ml to less than 0.5 ng/ml (STABENFELDT *et al.*, 1969 *a* ; THORBURN *et al.*, 1969), and oestrogens from about 5 pg/ml to 50 pg/ml (TERQUI *et al.*, 1974) (fig. 1).

Plasma LH presents minor variations during the whole cycle up to the onset of estrus (LAND *et al.*, 1973). In the majority of cases, LH surge starts between 0 and 10 hours after onset of estrous behavior ; it consists of an increase of the plasma level from 1-2 ng/ml to 60-120 ng/ml (GESCHWIND and DEWEY, 1968 ; NISWENDER *et al.*, 1968 ; PELLETIER *et al.*, 1968 ; WHEATLEY and RADFORD, 1969). The duration of the surge is 10-12 hours (NISWENDER *et al.*, 1968 ; PELLETIER and THIMONIER, 1969), and occurs about 26 hours before ovulation (WHEATLEY and RADFORD, 1969 ; CUMMING *et al.*, 1971).

A relationship between the quantity of LH released and the ovulation rate has not been found in cyclic ewes. However, the interval « onset of estrus-beginning of LH surge » is greater in females showing two ovulations than in those with only one ovulation (THIMONIER and PELLETIER, 1971). Similarly, this interval is greater in highly prolific breeds than in breeds of low prolificacy (LAND *et al.*, 1973).

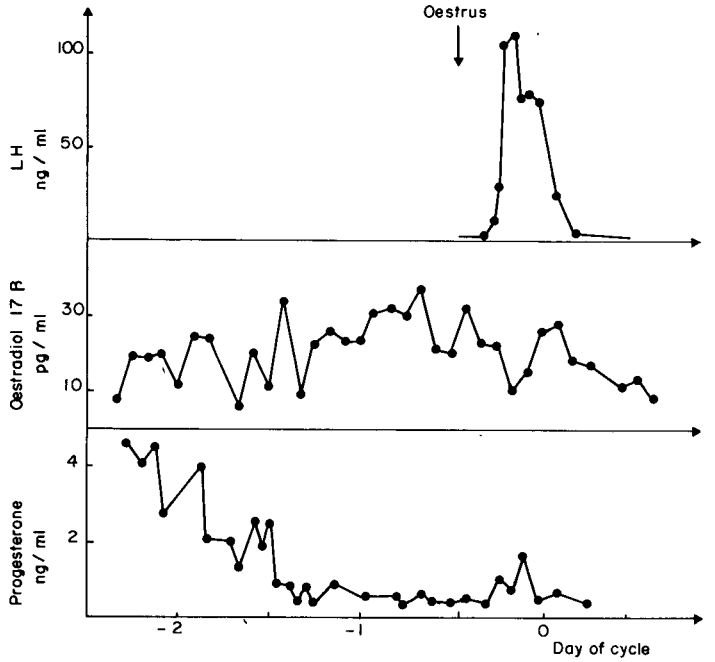

FIG. 1. — *Typical patterns of peripheral plasma LH, oestradiol and progesterone during the perioestral period in the ewe*
(From TERQUI *et al.*, 1974 and B. BOURSIER, 1974)

2. — Steroid and LH variations before ovulation in the cow and the sow

In the cow and sow, the chronology and the direction of variations affecting plasma steroids and LH are roughly similar to those described in the ewe. However, interspecific differences exist, and they reveal in a different manner the relationship between steroids and preovulatory LH release.

In the cow, plasma progesterone drop is as fast as in the ewe, and occurs between 72 and 48 hours before onset of estrus (SHEMESH *et al.*, 1968 ; STABENFELDT *et al.*, 1969 *b* ; HENRICKS *et al.*, 1971). The duration of the follicular phase seems to be under genetic control (LAMOND *et al.*, 1971). The existence of a preovulatory progesterone peak as described by AYALON and SHEMESH (1974) has not been confirmed by others (KATONGOLE *et al.*, 1973 ; LEMON *et al.*, 1975). The oestrogen pattern is more debatable. For some authors, an oestradiol peak occurs just before estrus (HENRICKS *et al.*, 1971), and for others, an oestrone peak precedes an oestradiol peak which occurs between 48 and 24 hours before estrus (ECHTERNKAMP and HANSEL, 1971 ; MASON *et al.*, 1972). However, the fluorometric methods used by the latter authors show values about 100 times greater than those found by radioimmunoassay. Meanwhile, the measurement of plasma free immunoreactive oestrogens suggests that 17β-oestradiol is not the main circulating oestrogen, although the identification and the roles of the different oestrogenic components is yet to be defined (LEMON and SAUMANDE, 1974). In fact, when the animal is bled frequently

during a collection period of several days before estrus, the idea of « peak » is not evident (KATONGOLE *et al.*, 1973 ; LEMON *et al.*, 1975), and plasma oestrogen increase is serrate, the maximum sometimes being reached after the onset of estrus. To evaluate the irregular increase, it has been suggested that the slope of the curve representing oestrogen rate increment be established as a function of time (HANCOCK *et al.*, 1970).

The LH peak is lower than observed in the ewe (20-50 ng/ml *vs* 50-120 ng/ml) (SCHAMS and KARG, 1969 ; HENRICKS *et al.*, 1970 ; SWANSON and HAFS, 1971) and begins at the same time as the first manifestations of estrus (SWANSON and HAFS, 1971 ; CUMMINS *et al.*, 1972 ; LEMON *et al.*, 1975). The latter authors observed the behavior of a small sample for a continuous period, and found that there is noticeable synchronization between acceptance of mating and beginning of LH peak. Finally, in zebu females (*Bos indicus*), a very short delay between onset of estrus and beginning of LH release has also been observed (CARR, 1972).

Differences in progesterone, oestrogen and LH variations are greater between the sow and the ewe. Due to the high number of corpora lutea, progesterone level reaches 35 ng/ml during the luteal phase (STABENFELDT *et al.*, 1969 *c*). Progesterone drop occurs 6-7 days before onset of estrus, creating a long follicular phase (STABENFELDT *et* al., 1969 *c* ; GUTHRIE *et al.*, 1972). On the contrary, oestrogens fluctuate between narrow limits (10-50 pg/ml), and mean values at the time of the peak occurring 1-2 days before estrus are only about two times the value observed during the remaining part of the cycle. It has also been shown that an oestrogen rise occurs after progesterone drop (HENRICKS *et al.*, 1972 ; GUTHRIE *et al.*, 1972). However, one of the most noteworthy endocrine characteristics in the sow is the low magnitude of the preovulatory LH peak, the plasma level only varying from 0.5-1 ng/ml to 3-4 ng/ml at maximum (NISWENDER *et al.*, 1970 ; RADFORD *et al.*, 1971). The length of the surge has not been exactly determined, but might last more than 10 hours (HENRICKS *et al.*, 1972). The low quantity of LH released at estrus in a species where the ovulation rate is high, clearly indicates that the number of corpora lutea is not correlated only with preovulatory surge intensity.

Finally, while the succession of endocrine events before ovulation is similar in the three species, the respective roles of oestrogens and progesterone in initiating LH release cannot be exactly defined.

II. — ROLES OF OESTRADIOL AND PROGESTERONE IN INITIATING LH RELEASE AND THEIR USE FOR ESTRUS CONTROL IN THE EWE

1. — *Roles of oestradiol and progesterone*

Drop of plasma progesterone, then oestrogen increase before preovulatory LH release, led to three different hypotheses for domestic animals : *a*) decrease of plasma progesterone is the signal which initiates LH release, *b*) increase in plasma oestrogens only is responsible for this surge, *c*) a third hypothesis considers both

points *a* and *b* as necessary. The findings are most conclusive in the castrated ewe where a progesterone treatment followed by oestradiol benzoate injection not only restores estrous behavior, but induces a « preovulatory »-type surge (PELLETIER and SIGNORET, 1969 ; RADFORD *et al.*, 1969). The first hypothesis was discarded when it was later shown that various treatments with progesterone were unable to induce LH discharge. However, when given at the same time as oestradiol, progesterone inhibited the inducing effect of oestradiol (fig. 2). Finally, it was found

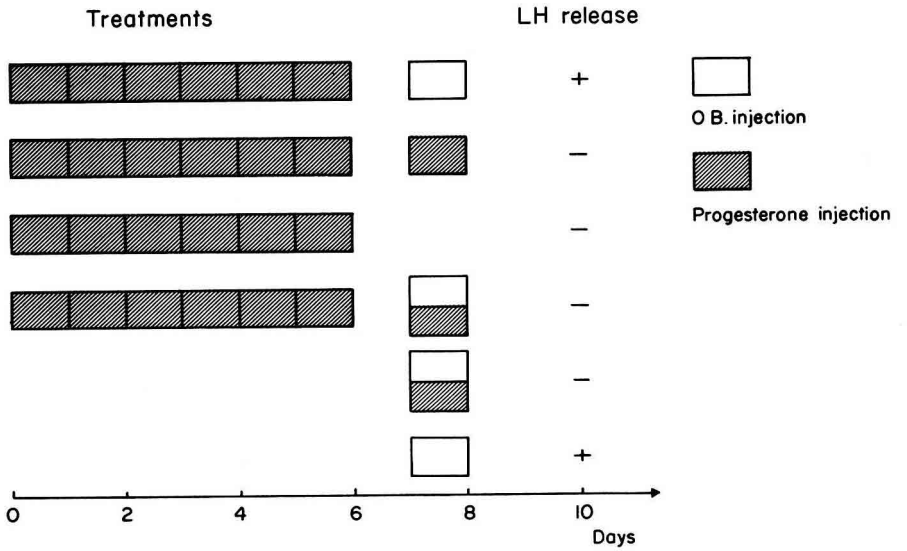

FIG. 2. — *Influence of various oestradiol benzoate and progesterone treatments on induction of a « preovulatory-type » LH release in the castrated ewe*

(From PELLETIER and SIGNORET, 1970)

+ : obtention of LH release (70 to 90 p. 100 of females) at day 9 or 10 of the artificial cycle.
— : no LH release (100 p. 100 of females)

that an injection of oestradiol benzoate alone was sufficient to induce LH release in about 90 p. 100 of ewes (PELLETIER and SIGNORET, 1970). These facts were confirmed in castrated ewe (SCARAMUZZI *et al.*, 1971) and in the ovariectomized cow (HOBSON and HANSEL, 1972 ; SHORT *et al.*, 1973). Thus, oestradiol was considered as the essential agent in initiating preovulatory LH surge. However, while the hypothesis of a *per se* effect of progesterone decrease (SNOOK *et al.*, 1971) was discarded, it was thought that progesterone could have an indirect beneficial role on the surge owing to its negative feedback effect limiting tonic LH release thereby allowing reconstitution of pituitary LH stock during the luteal phase.

2. — *Effects of progesterone or its derivatives on control of LH surge*

Since DUTT and CASIDA (1948) showed that intramuscular injections of progesterone prevented ovulation in the cyclic ewe, this hormone, and particularly some of its synthetic derivatives, have been used to temporarily inhibit estrus and ovula-

tion and thus to synchronize a group of females. Fluorogestone acetate (FGA, Searle), given by vaginal route (ROBINSON, 1965) prevents LH surge during the duration of the treatment. It occurs later spontaneously, but the quantity of LH released represents only 60 p. 100 ($P < 0.01$) of that released under normal conditions (PELLETIER and THIMONIER, 1969). CUMMING *et al.* (1971) have not found any differences between these two groups, but the authors did not calculate the intensity of LH surge.

In the cyclic cow, treatment with melengestrol acetate was not found to modify preovulatory LH surge (WETTEMAN and HAFS, 1973) ; curiously, it increased the plasma basal level by 100 to 150 p. 100 (HILL *et al.*, 1971 ; RANDEL *et al.*, 1972).

In the ewe treated during the seasonal anestrous period, progestagen treatment is not followed by spontaneous LH release. Consequently, under practical conditions, a progestagen treatment must be associated with a treatment to induce LH release.

3. — *Effect of oestradiol on induction of LH release*

The injection of oestradiol induces a preovulatory LH surge in the anestrous ewe (GODING *et al.*, 1969 ; RADFORD *et al.*, 1971 ; BECK and REEVES, 1973). Oestradiol acts similarly in the ewe during the sexual season, but only during a short period at onset of the estrous cycle, 3-4 days after estrus when the progesterone level is low (BOLT *et al.*, 1971 ; SYMONS *et al.*, 1973). These results confirm those of PIPER and FOOTE (1968) based on ovulation. In the female, oestradiol may induce a preovulatory-type of LH surge as early as 38 days of age (LAND *et al.*, 1970). The interval between oestradiol intramuscular injection and beginning of LH surge is about 8-12 hours, and according to BECK and REEVES (1973) is independent of the dose used in the range of 12.5-200 µg. According to the same authors, the magnitude of the LH peak is not related to the quantity of oestrogen given. However, oestradiol injected at the end of a progestagen treatment tends to reduce fertility in ewes (ROBINSON *et al.*, 1970). This may be due to a synergistic negative feedback effect with the progestagen at the hypothalamo-pituitary level. These results, and the need to induce follicular development in animals in anestrus, have led us to examine other LH release inducers.

4. — *PMSG as an inducer of LH release*

Inducing follicular growth, LH release and finally superovulation, PMSG is intensively used in ovine (THIMONIER and COGNIE, 1971) and bovine (MAULÉON *et al.*, 1970 ; BELLOWS and SHORT, 1972) species. Correlations between oestrogen production and intensity of LH release ($r = + 0.61$, $P < 0.01$), as well as between quantity of LH released and ovulation rate ($r = + 0.71$, $P < 0.01$) have been demonstrated in cattle (SAUMANDE and PELLETIER, 1975).

After interruption of progestagen treatment (vaginal FGA) in the cyclic ewe, PMSG induces a surge of LH similar to that in natural conditions (PELLETIER and THIMONIER, 1969). However, some difficulties remain. In addition to the appearance of a refractory period leading to reduced ovulation rate following its repeated use (HAFEZ *et al.*, 1965 ; HULET and FOOTE, 1969), this hormone, reinforced or not

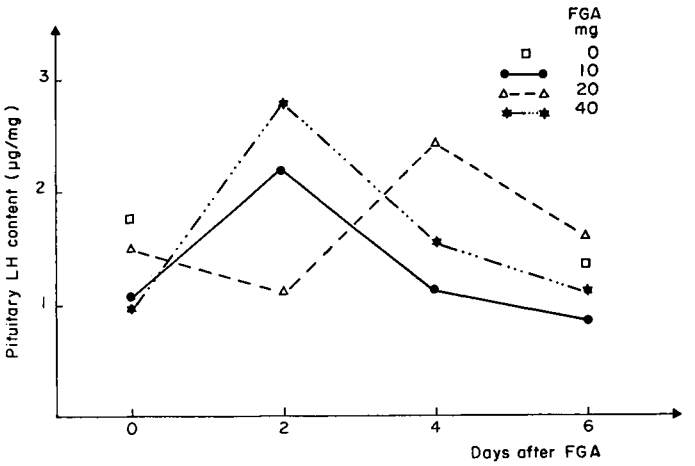

FIG. 3. — *Variations in pituitary LH content after various progestagen treatments* (FGA, 12 days) *in the lactating ewe during the period of seasonal anoestrum.*
Start of treatment 40 days after parturition ;
three females per group sacrificed at each time of slaughter
(PELLETIER and THIMONIER, unpublished results)

TABLE I

Variation of intensity of preovulatory LH surge
in lactating ewes during seasonal anestrous as related to the interval
« End of progestagen treatment-PMSG injection »
(PELLETIER and COGNIE, unpublished data)

Grp. Phys. State	*n*	FGA treatment length (1) (days)	FGA-PMSG (2) interval (hours)	LH release (3)	
				mm²	p. 100
1. Dry ewe	7	12	0	3 773 ± 378	100
2. Lactating ewe	7	12	0	2 892 ± 350	76.6
3. — —	7	6	0	2 734 ± 267	72.5
4. — —	7	6	12	3 142 ± 126	83.3
5. — —	7	6	24	2 966 ± 487	78.6
6. — —	7	6	36	2 270 ± 223	60.2
7. — —	7	6	48	2 189 ± 261	58.0

(1) FGA : 40 mg.
(2) PMSG : 600 IU (dry ewes) and 750 IU (lactating ewes).
(3) LH release estimated from the area under the LH curve.
(4) All females ovulated except two in grp. 6.

by oestrogens, induces an LH surge in lactating ewes during seasonal anestrus which is only 65 p. 100 of that in dry ewes (PELLETIER and THIMONIER, 1973).

A study of variation of pituitary LH content in lactating females treated with progestagen in the non-sexual season indicates that the content increases after the treatment is discontinued (fig. 3). We have tried to improve PMSG efficiency in lactating females by studying the influence of the interval « withdrawal of progestagen treatment-injection of PMSG » on the intensity of LH release (table 1). As compared to an interval equal to zero, a 12-hour interval slightly improves the quantity of LH released; however, it represents only 83 p. 100 of that observed in dry ewes (PELLETIER and COGNIE, unpublished results). When this interval is greater than 24 hours, LH release is reduced. The latter result and the difficulty in using homogeneous lots of PMSG have led us to examine the effect of other LH-release inducers, namely the recently synthesized LH-releasing factor (LRF) (MATSUO *et al.*, 1971).

5. — *LRF as inducer of LH release*

The injection of LRF induces a LH surge in ewes (REEVES *et al.*, 1970, 1972; CUMMING *et al.*, 1972 ; WHITE *et al.*, 1973 ; RIPPEL *et al.*, 1974 ; SEGERSON *et al.*, 1974), cows (ZOLMAN *et al.*, 1973 ; KALTENBACH *et al.*, 1974) and sows (BAKER *et al.*, 1973;

TABLE 2

Effect of lactation on intensity of preovulatory LH surge induced in seasonal anestrous ewe

	n	Interval PMSG-LRF (hours)	LH release (ng/ml/1 h) (1)	Peak value (ng/ml)
Dry ewes	6	24	313 ± 47.0	111.5 ± 19.1
	6	30	279 ± 44.3	104.7 ± 12.9
Lactating ewes	6	24	169 ± 30.0	68.0 ± 9.0
	6	30	177 ± 29.7	76.6 ± 10.9

(1) Mean ± S. E. M.

CHAKRABORTY *et al.*, 1973). Preovulatory LH release similar to that of a normal estrous cycle is obtained in the dry ewe, previously treated with progestagen in seasonal anestrus and given an LRF injection 24 hours after a reduced PMSG injection (PELLETIER, 1974). We thought that LRF would quantitatively restore induced LH release in the lactating ewe during seasonal anestrus. However, induced LH release, in these conditions, represents only 60 p. 100 of that in dry ewes (PELLETIER, 1974) (table 2). As pituitary LH content of lactating ewes does not differ greatly from dry ewes, we must conclude that LH release is not due to simple LRF effect, but is a result of interaction between the LRF and other hormones.

III. — FEEDBACK EFFECT OF STEROIDS AT HYPOTHALAMIC AND PITUITARY LEVELS

1. — *At the hypothalamic level*

It is admitted that ovarian steroid production, which is stimulated by gonadotropins, exerts a feedback effect at the hypothalamic level. However, this general concept largely lacked physiological or direct experimental demonstration by plasma LRF assay until recently. In 1970, SCHNEIDER and MCCANN presented a scheme of oestradiol negative feedback effect on LRF release via synthesis of a regulating protein, but these authors did not consider the positive feedback effect at the time of preovulatory surge. This effect, however, is highly probable since a 50 p. 100 decrease in hypothalamic LRF content (CRIGHTON *et al.*, 1973) and a plasma LRF increase from less than 0.5 ng/ml to 6 ng/ml (KERDELHUE and JUTISZ, 1972) are simultaneous with preovulatory LH surge. Furthermore, RADFORD and WALLACE (1974) have shown that in castrated ewes, induction of LH release by oestrogen is delayed while animals were under anesthesia. This clearly suggests a central oestradiol effect.

While the mode of positive oestradiol action at the hypothalamic level is not exactly known, sexual steroids could exert an inhibiting effect via decrease in LRF synthesis, as it has been suggested for testosterone in ram (PELLETIER, 1970). After a 6-day treatment with the FGA (40 mg) administered by vaginal route, a 35 p. 100 decrease in LRF hypothalamic content is observed in the dry ewe (PELLETIER and THIMONIER, 1972). On the other hand, if the same dose of FGA is given for 12 days, a 30 p. 100 increase in LRF hypothalamic content is obtained. This could result from rebound effect, namely increased synthesis following the period of inhibition. In present conditions, such a phenomenon is possible since there is a daily decrease of about 16 p. 100 in the quantity of FGA released from the vaginal sponge (MORGAN *et al.*, 1967). However, the same treatment given to lactating females induces a decrease in hypothalamic LRF content of 15 and 32 p. 100 for 20 and 40 mg of FGA, respectively, even after 12 days of treatment (PELLETIER and THIMONIER, 1972). It is unlikely that anestrus would be due to a lack of LRF in the hypothalamus (JACKSON *et al.*, 1971), but would more probably result from the absence of a signal for preovulatory surge.

2. — *At the pituitary level*

In 1970, REEVES *et al.* showed that LH release induced by purified LRF was greater when the injection was given to ewes in estrus than to ewes at other stages of the estrous cycle. These authors concluded that pituitary responsiveness to LRF is modified by circulating steroids. It has been further shown that oestradiol increases pituitary responsiveness to LRF in the ewe (REEVES *et al.*, 1971), cow (ZOLMAN *et al.*, 1974), woman (YEN *et al.*, 1972) and rat (ARIMURA and SCHALLY, 1971). The role of progesterone, however, is less clear; it has been found to block LH release induced by intrapituitary infusion of LRF in the rabbit (HILLIARD *et al.*, 1971),

but not in the ewe (CUMMING *et al.*, 1972). In the latter case, however, progesterone given by intravenous infusion was not measured in the blood to check the level during infusion.

Thus, we injected ewes with 25 μg of synthetic LRF at day 4, 8, 12 or 16 of the estrous cycle ; 17β-oestradiol and progesterone plasma levels were measured before LRF injection. Mean LH response for days 4, 8 and 12 is 39, 16 and 13.5 p. 100, respectively, of that observed on day 16 (fig. 4) (THIMONIER *et al.*, 1974). It appears

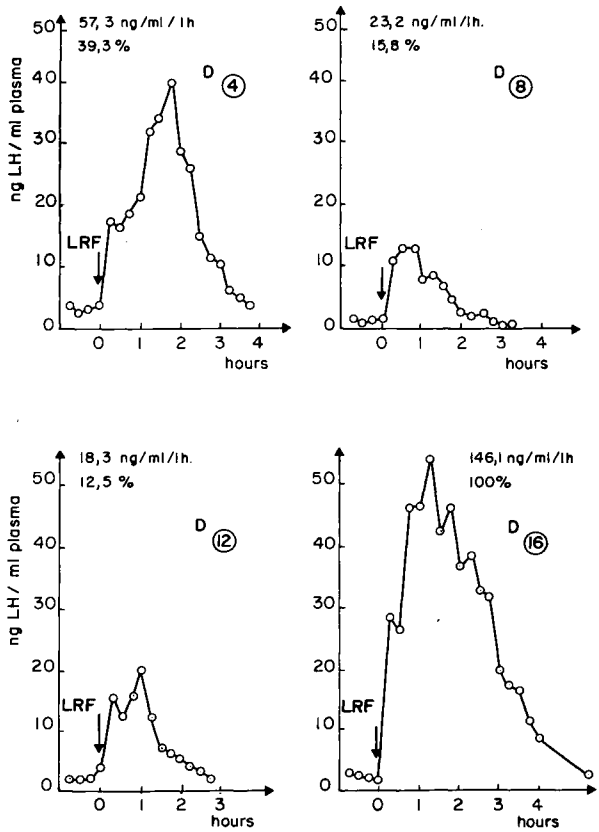

FIG. 4. — *Variation of LH response to LRF in a typical ewe injected at day 4, 8, 12 or 16 of the oestrous cycle* (IV injection of 25 μg LRF ; 3 ♀/group)
(From THIMONIER *et al.*, 1974)

that intensity of LH release is better correlated with the oestradiol/progesterone ratio than with the oestrogen or progesterone plasma level. In the present experiment, the correlation coefficient between the logarithm of LH response to LRF and the oestradiol/progesterone ratio is + 0.97 ($P < 0.05$). SYMONS *et al.* (1974) and RIPPEL *et al.* (1974) found no variation in LH response to LRF during the ewe estrous cycle, but it may be that these authors did not choose the times of maximal oestradiol/progesterone ratio variation during the cycle. If the plasma oestrogen/progesterone ratio is of importance in order to induce LH release with LRF, a difference in pituitary responsiveness to LRF could explain that releasing-factor in lactating ewes

has a weaker effect than in dry ewes. In fact, COGNIE *et al.* (1974) have shown that in lactating ewes pretreated with progestagen during the seasonal anestrus, the 17β-oestradiol plasma level was lower than in dry ewes treated in the same conditions.

Similarly, it is likely that a variation in pituitary responsiveness to LRF could explain the cessation of preovulatory release. The interruption would not be due to a lack of LRF since this would be released after the end of LH surge (KERDELHUE and JUTISZ, 1972 ; FOSTER *et al.*, 1974). On the contrary, we previously suggested (PELLETIER and SIGNORET, 1969, 1970) that the greater duration of oestrogen-induced LH release in the castrated ewe as compared to the entire female could be due to lack of negative feedback in absence of ovarian steroids. It would be interesting to find out if such a feedback mechanism acts at the pituitary level.

CONCLUSION

The dates of the studies cited clearly indicate the extent of recent progress, since 90 p. 100 of the references included date from the last 6 years. Among the major facts recently exposed, it is seen that the respective roles of oestrogens and progesterone in initiating LH release have been determined. Furthermore, the purification and synthesis of LRF permit the demonstration of a direct steroid feedback effect at the pituitary level, thus greatly improving our knowledge of the relationships between hypothalamus, pituitary and gonads. Finally, plasma LH and steroid patterns have been described during the estrous cycle of a number of species.

The present orientation of research should be to improve our knowledge of hypothalamus « physiology », *i.e.* variations in LRF synthesis and release during the cycle, and the external and internal factors of regulaion.

These fundamental improvements in domestic animals will undoubtedly have a strong influence on the techniques of reproduction control.

Colloque : Control of sexual cycles in domestic animals
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RÉSUMÉ

INTERACTIONS ENTRE LES STÉROÏDES OU LES PROGESTAGÈNES ET LA DÉCHARGE DE LH

Il est admis aujourd'hui que la décharge préovulatoire de LH chez les mammifères domestiques est reliée à une sécrétion préalable d'œstrogènes par l'ovaire. Une augmentation d'œstradiol-17β dans le sang précède le pic de LH dans les conditions naturelles pendant la saison

sexuelle, mais une telle décharge peut être également induite expérimentalement par injection d'œstrogène soit chez la Brebis en anœstrus soit chez la femelle castrée. Ainsi l'injection de 50 µg de benzoate d'œstradiol induit chez la brebis castrée, dans 90 p. 100 des cas un pic de LH de même amplitude mais de durée plus longue (16 h 30 *vs* 10 h 30, $P < 0,01$) que celui observé lors du cycle œstrien. Inversement, la progestérone, bien qu'ayant probablement un effet positif indirect sur la décharge préovulatoire de LH, apparaît essentiellement inhibitrice dans les conditions expérimentales : aucune femelle castrée ne présente un pic de LH soit après une injection (25 mg) soit après une série d'injections. De plus la progestérone empêche dans tous les cas (4 à 8 femelles par groupe) l'effet positif de l'œstradiol.

On connaît mal le mode d'action des stéroïdes au niveau de l'hypothalamus, mais il est probable que l'effet positif de l'œstradiol sur la décharge de LH et l'effet négatif de la progestérone sont exercés à ce niveau. L'influence des œstrogènes est suggérée par une diminution de 50 p. 100 du contenu hypothalamique en LRF lors du pic de LH, interprétée comme une libération massive de ce facteur de décharge. L'effet de la progestérone peut être déduit d'une étude effectuée chez la brebis allaitante où le progestagène (FGA) a été trouvé provoquer une diminution du contenu hypothalamique en LRF mais sans pic de LH concomitant. Cette diminution atteint 15 et 32 p. 100 du contenu hypothalamique de brebis témoins chez des femelles traitées pendant 12 jours respectivement avec 20 ou 40 mg de FGA.

Une démonstration encore plus récente de l'interrelation entre les stéroïdes et l'activité hypothalamo-hypophysaire est la variation de la sensibilité de l'hypophyse au cours du cycle œstrien. Ainsi chez la Brebis, une injection intraveineuse de LRF induit une décharge de LH dont l'intensité varie en fonction du moment du cycle où cette injection est effectuée. La réponse moyenne de LH après une injection de 25 µg de LRF est respectivement de 57, 23, 18 et 146 ng/ml/1 h lorsque le LRF est administré à des brebis aux jours 4, 8, 12 ou 16 du cycle œstrien. Cette réponse de LH au LRF est corrélée avec le rapport œstrogène/progestérone dans le sang ($r = 0,97$, $P < 0,05$) qui apparaît ainsi réguler l'effet du LRF au niveau hypophysaire.

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