final order. Is the binaural matching of best frequencies accompanied by any form of cooperative reorganization within the superior olive itself, or is it achieved solely by selective specificity of the regenerating afferents for their former target cells? If reorganization is largely a result of the specificity of a regenerating afferent for its target, do regenerating fibers synapse directly and unerringly on their former target cells, or do they locate an appropriate postsynaptic neuron only after a period of trial connections? Under our experimental conditions, the reformation of functional synapses can occur 5 to 6 weeks after the nerve is cut (*13*). Hence, the regenerated nerve had been in contact with central cells for at least 6 weeks before the data in this study were collected. But these questions could be pursued by documenting the similarity of the best frequencies for binaural cells in the superior olive early in the reinnervation process.

In other sensory systems, the study of regenerative processes has been instrumental in yielding insights into the mechanisms that guide the initial formation of connections during ontogeny (*12*). The preparation we have developed should lead to such insights in the auditory system, where, at present, there are few studies of the dynamics of formation of central connections during development (*14*).

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Brain 5β-Reductase: A Correlate of Behavioral Sensitivity to Androgen

Abstract. *Testosterone is converted in the dove* (Streptopelia risoria) *brain to 5β-reduced metabolites that do not affect behavior. In long-term castrated birds, which are relatively insensitive to the behavioral effects of testosterone, the activity of preoptic 5β-reductase is increased. The increase, which is specific to the preoptic area, is reversed by estrogen. Inactivation of testosterone by 5β-reduction may be involved in the control of brain sensitivity to androgen.*

Hormones affect sexual behavior by direct action on the brain (*1*). Their action is influenced in two ways: either the hormone itself can change in amount and availability or the sensitivity to hormone of the tissues mediating the behavior can change. Although sensitivity to androgen is known to be influenced by the genetic constitution of the individual (*2*), exposure to hormones during early development (*3*), environmental stimuli (*4*), and hormonal condition in adulthood (*5*), the brain mechanisms involved have not been identified. In the dove *Streptopelia risoria*, male courtship depends on the action of androgen on the preoptic-anterior hypothalamus (AHPOA) of the brain (*6*). The effectiveness of implants of testosterone propionate (TP) in the AHPOA declines with time after the male is castrated, suggesting that sensitivity to androgen changes according to hormonal status and that target cells in the AHPOA participate in the change.

Metabolism to active hormones is an important step in the action of androgen on target cells (*7*). In addition to converting testosterone to 17β-estradiol and 5α-dihydrotestosterone (5α-DHT), both of which have behavioral effects, the AHPOA of the male dove is also active in producing 5β-androstanes, 5β-dihydrotestosterone (5β-DHT), and the two corresponding diols (3α- and 3β-, 17β-diols) which have no behavioral effects (*8*) and appear to have no androgenic action in other species (*9*). The evidence (*8*) suggests strongly that the 5β-reduction pathway is part of a steroid inactivation mechanism that could influence the concentration of active androgen in the AHPOA.

Recently, we found that formation of 5β-DHT is increased in the preoptic area (POA) of long-term castrated doves compared to intact males (*8*). This is consistent with the view that testosterone inactivation increases with decline in behavioral sensitivity to androgen. Measurement of total 5β-reduction is required to test this hypothesis. Because there may have been individual differences in the effects of interaction with the female, 5β-reduction of testosterone was very variable in males tested for courtship. Therefore, we have examined the possibility that decreased behavioral sensitivity to androgen is related to increased 5β-reduction of testosterone by measuring the male vocal behavior, perch calling, which is highly sensitive to androgen and is displayed independently of the female (*10*). We report here that testosterone inactivation by 5β-reduction is markedly increased in the POA of long-term castrated doves which are relatively unresponsive to the behavioral action of testosterone. To our knowledge, this is the first report of a change in brain metabolism of a sex hormone, which can be related to both hormonal condition and the behavioral effectiveness of the hormone.

We measured total 5β-reduction (*11*) in intact, sexually active males, two groups of short-term (30-day) castrates, and three groups of long-term (200-day) castrates ($N = 6$ in each group). The short-term castrates were treated with

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TP or saline, the long-term castrates with TP, diethylstilbestrol (DES), or saline. Treatment began on days 31 or 201 after castration and continued for 12 successive days. The presumed target areas for testosterone, the POA and anterior hypothalamus (AHA), were sampled separately, because autoradiography indicates differences in steroid uptake between them; the POA concentrates [^{3}H]-testosterone or estradiol more intensely than the AHA (*12*). The effectiveness of TP in the castrated groups was assessed without disturbing the animals by measuring perch calling in the birds' home cages (*13*).

Preoptic samples from saline-treated castrates showed a progressive increase in total 5β-reduction with time after castration (Fig. 1b). Total 5β-reduction in long-term castrates was significantly higher than in intact males. In contrast to the POA, there was no difference between the groups in 5β-reduction within the AHA. Therefore, the long-term castrates showed not only an increased 5β-reductase activity in the androgen-sensitive POA but also an anatomical separation in the amount of 5β-reduction between the POA and AHA that is not present in the sexually active, intact male. The latter result indicates that a long-term androgen deficit results in a distinct difference in enzyme activity between nuclei that are commonly regarded in birds and mammals to be part of a single androgen-sensitive brain complex—the AHPOA. Testosterone propionate decreased 5β-reduction in the POA of both short- and long-term castrates, but in the long-term castrates 5β-reduction was still above intact levels (Fig. 1b). Enzymatic activity in the AHA was not affected significantly, which confirms the selectivity of the effect.

The behavioral data showed a parallel to the level of 5β-reduction in the POA. Long-term castrates with the highest POA 5β-reductase activity were less responsive to TP relative to the intact group in both vocal behavior and suppression of 5β-reduction (Fig. 1). The short-term castrates did not differ significantly from the intact group in either 5β-reductase activity or durations of perch calling. Although the data indicate an inverse relation between 5β-reduction and behavioral response to TP, an important question remains: Can the increase (about twofold) in preoptic 5β-reduction account for reduced behavioral response to androgen? Two points require consideration. First, although discrete POA samples were used in our study, the proportion of androgen target cells in this area is probably low (*14*). Therefore, if the increase in 5β-reduction is restricted to these androgen target cells, as is suggested by comparison of enzyme activity with adjacent brain areas, it is clearly underestimated. Second, the key enzyme in the inactivation pathway, 5β-reductase, occurs only in the nonnuclear fraction of dove brain cells (*8*). We have shown recently using cell fractionation that 5β-reductase is, as in mammals (*7*), a soluble cytoplasmic enzyme. Therefore, 5β-reduction is likely to occur soon after testosterone enters the target cell and competes both with conversion of testosterone to other active metabolites and binding to specific high-affinity receptors. A similar competition between binding to the androgen receptor and metabolism by 3α-hydroxysteroid dehydrogenase has been shown to occur for 5α-dihydrotestosterone in the rat prostate (*15*). Accordingly, an increase in 5β-reduction may have marked effects on alternative pathways of testosterone utilization.

In the male dove, aggressive components of courtship, as well as perch calling, are specifically testosterone-dependent, whereas the nest-oriented courtship pattern, nest soliciting, appears to be mediated by estrogen acting on the AHPOA (*16*). An intriguing question raised by our findings is whether estrogen derived from testosterone, in addition to its specific effects on nest-oriented courtship, may also play a part in the regulation of testosterone-dependent brain mechanisms of behavior. The natural estrogen 17β-estradiol decreased the formation of 5β-DHT in long-term castrates to concentrations in intact males (*8*). The synthetic estrogen DES substantially reduced total 5β-reduction in the POA (Fig. 1b). In contrast to estradiol, DES does not cross-react with androgen receptors in the brain (*17*). Therefore, the 5β-reduction pathway is estrogen-sensitive. Suppressive effects of androgen are likely to be due to an action of estradiol derived by aromatization within the brain, because the POA is very active in converting testosterone to estradiol (*18*). If estrogen influences testosterone inactivation, as we suggest, the marked increase in preoptic 5β-reductase activity of long-term castrates (Fig. 1b) may be due to the absence of suppressive effects of estradiol. Similarly, the relative ineffectiveness of TP therapy in decreasing 5β-reduction of long-term castrates (Fig. 1b) may be a result of decreased preoptic aromatase activity. Results indicate that testosterone-mediated induction of aromatase activity (*19*) is diminished in long-term castrates. The suppressive effect of estradiol or DES does not appear to be due to the direct action of these compounds on 5β-reductase activity, because in vitro incubation of preoptic tissue with 10 n*M* [^{3}H]testos-

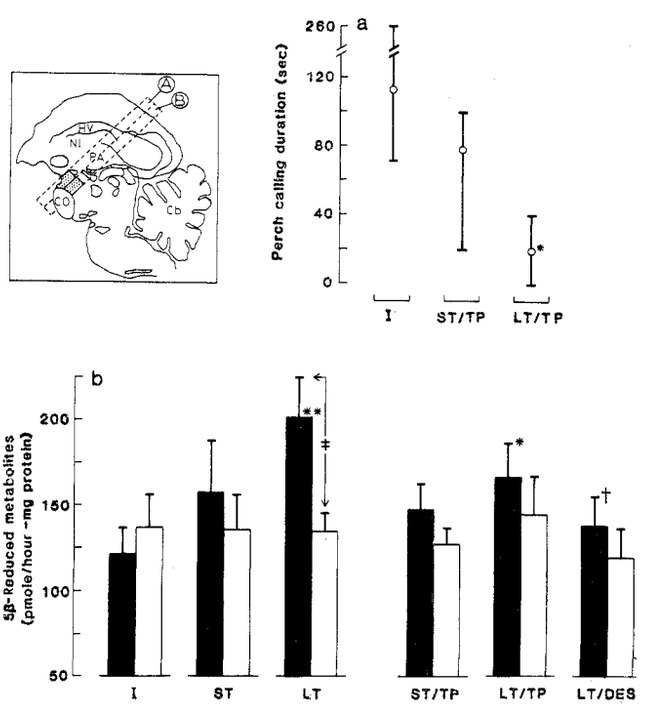

Fig. 1. (a) Durations of perch calling (medians and ranges) of intact males (*I*) and short-term (*ST*) and long-term (*LT*) castrated doves treated with testosterone propionate (*TP*) [intact group compared with castrated groups (*P = .006, Mann-Whitney U test, two-tailed)]. (b) Total 5β-reduced metabolites (vertical bars show ± standard error of the mean) in the POA (shaded bars) and the AHA (unshaded bars). Symbols: *I*, intact males; *ST* and *LT*, short- and long-term castrates treated with saline; *ST/TP* and *LT/TP*, short- and long-term castrates treated with testosterone propionate; and *LT/DES*, castrates treated with diethylstilbestrol. For intact males compared with saline- and hormone-treated castrates, *P = .025, **P = .01; long-term castrates compared with hormone-treated groups, †P = .025; POA samples compared with AHA within each group, ‡P = .025. Boxed insert shows a parasagittal view of dove brain with coronal slices A and B (dotted lines) for POA and AHA samples (stippled areas).

terone and a 100-fold excess of estradiol or DES does not diminish the amount of testosterone (approximately 20 percent) converted to 5β-reduced metabolites. Lack of effect is not due to assay conditions: spiroxenone (20-spirox-4-ene-3-one), a specific inhibitor of ring A reduction, decreased formation of 5β-reduced metabolites by more than 50 percent.

The classical model of steroid hormone action on brain target cells requires that the hormone binds to cytoplasmic receptors and is translocated to the cell nucleus where initiated genomic effects are translated into neuronal changes (*20*). Whether events of this type mediate androgen action on behavioral mechanisms is still uncertain. In the dove, there appears to be no decrease in nuclear uptake of testosterone that could account for behavioral insensitivity to androgen (*5*). However, our evidence indicates a significant increase in 5β-reductase activity, and such activity is likely to compete both with the conversion of testosterone to active metabolites and with the binding of testosterone to receptors. We suggest, therefore, that inactivation by 5β-reduction influences behaviorally effective androgen concentrations within target cells of the POA. This mechanism could be important in determining brain sensitivity to circulating androgen under changing hormonal conditions. At present, we do not know how 5β-reductase is controlled, but the evidence points to a role for an aromatization product.

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10. The stereotyped perch call is uttered repetitively by the male in visual isolation. This behavior is specifically androgen-dependent; estrogen is ineffective (J. B. Hutchison, T. Steimer, R. Duncan, *J. Endocrinol.*, in press). As in male courtship behavior, the effectiveness of intrahypothalamic androgen on perch calling declines with time after castration (J. B. Hutchison and L. Innes, in preparation).
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13. Males were observed for vocal behavior (perch calling) for 10 minutes, beginning at 0900 hours. Behavior was recorded continuously by means of the WRATS computer-compatible system. The longest of the daily durations of calling (peak durations) were calculated for each bird.
14. When [^{3}H]testosterone of high specific activity is injected intramuscularly, uptake of radioactivity in the POA is very low compared to the pituitary in the dove (T. Steimer and J. B. Hutchison, in preparation), suggesting that relatively few cells take up the hormone.
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Aseismic Uplift in California

We disagree with several of the arguments cited by Jackson *et al.* in support of their view that "the inference of widespread aseismic uplift in southern California is not justified" (*1*). Specifically, the striking correlation shown in figure 1 of Jackson *et al.* (*1*) is an artifact of the construction, the rod calibration data are atypical, the cited regression techniques are of doubtful value, and the geologically and geodetically determined uplift rates are inappropriately compared.

First, figure 1 of the report by Jackson *et al.* (*1*) offers the most visually impressive suppport for their conclusion that signal (tilt) and topography are correlated at both short and long wavelengths. However, this illustration provides no support for this conclusion. For example, we show by means of the same method used in generating figure 1 of Jackson *et al.* (*1*) that a similarly strong correlation is produced through the application of a uniform tilt (and hence devoid of short wavelength components) to an actual terrain profile characterized by unequal bench mark spacing (*2*).

Second, the rod calibration data presented by Jackson *et al.* (*1*) exaggerate the magnitude of the normal rod error and, by implication, misrepresent the validity of the correction procedures designed to accommodate these errors. Rod calibration data are represented in figure 3 of the Jackson (*1*) report as rod "strain," a procedure that suggests that the error is distributed as a step function and thus distorts the error in the region of the calibration points. Moreover, by representing an error of 0.02 mm in the 0.2-m footpiece (or ungraduated part) of the rod as "strain," Jackson *et al.* (*1*) imply that the error over a nominal length of 1 m would amount to 0.10 mm (1×10^{-4}). However, the most misleading distortion introduced into this particular argument is the characterization of the identified rod, 312-268, as "a typical rod used in the southern California study" (*1*). The validity of the rod excess, which is derived from the calibration data and permits the conversion of the field measurements into corrected observed elevation differences, depends on the distribution of the error over the length of the rod. The less linear this distribution, the less valid the correction. Linear regressions of cumulative rod errors on cumulative nominal lengths computed for the first 100 calibrations in the National Geodetic Survey rod and instrument file read to the nearest 0.01 mm showed that these errors are indeed generally linearly distributed (*2*). Ninety percent of the standard deviations about the regression lines were 0.02×10^{-3} m (2×10^{-5}) or less; the 1965 and 1966 calibrations for rod 268 yielded the larg-

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