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Pituitary Function Following Treatment with Reproductive Toxins

by Ralph L. Cooper,* Jerome M. Goldman,* and Georgia L. Rehnberg*

Appropriate regulation of reproductive processes are dependent upon the integrity of pituitary function. In this selected review, we evaluate the evidence that certain environmental compounds exert their effect on reproductive function via a direct action on the pituitary gland. We also discuss examples of changes in pituitary hormone secretion that occur in response to changes in neuronal or gonadal control of the pituitary. A limited number of studies suggest that measures of pituitary hormone secretion provide an early and sensitive measure of a compound's potential effects on the reproductive system. However, the most striking aspect of this area is the sparse and inconsistent information describing pituitary function following exposure to environmental pollutants.

Introduction

The cells within the pituitary must respond to continuously changing CNS and gonadal signals and provide the appropriate moment-to-moment responses. As such, changes in pituitary hormone secretion serve to integrate a number of the complex mechanisms associated with successful reproduction. It would, therefore, be expected that environmental compounds which affect reproductive performance may do so because pituitary function is altered. However, studies of reproductive toxins frequently ignore measures of pituitary or hypothalamic-pituitary function in response to treatment. Theoretically, certain classes of compounds could affect pituitary function directly by altering cellular activity and hormone secretion. Other compounds could affect pituitary function indirectly by modifying CNS and/or gonadal hormone stimulation of the cells. Still others could have both direct and indirect effects. In this selected review, we shall examine the evidence that pituitary hormone secretion is altered by reproductive toxins and the extent to which such changes represent the primary mechanism through which the toxin influences reproductive capacity.

There is substantial support for a direct pituitary effect for estrogenic compounds, while therapeutic drugs and substances of abuse affect reproduction principally by modifying CNS function. Also, there is good evidence that certain compounds such as the pesticide dibromochloropropane (DBCP) and the nonsteroidal antifertility agent 1,2-dimethane sulfonate (EDS) exert their primary influence on the testis and as a consequence alter pituitary activity (*1–3*). Nevertheless, there is little substantive information describing the site of the primary effect of a variety of other xenobiotics or toxic metal cations on brain-pituitary-gonadal function, even though many of these compounds are known to modify reproductive capacity.

Estrogenic Compounds

Many environmental compounds have been found to possess estrogenic actions. Those that have received the most attention over the last two decades, in terms of their effect on the reproductive system, include the nonsteroidal estrogen, diethylstilbestrol (DES), and certain chlorinated hydrocarbon pesticides (chlordecone and methoxychlor) (*4*). DES, methoxychlor and chlordecone, as well as the mycotoxin zearalenone (*5*), have all been reported to cause infertility in adult laboratory and domestic animals. Exposure of newborn female rats to estrogens markedly perturbs reproductive processes in later life, presumably by altering the development of the neural mechanisms regulating gonadotropin secretion. DES, methoxychlor, chlordecone, or zearalenone administered during the critical periods of sexual differentiation will also cause persistent alterations in reproductive development (*6–9*). In humans, administration of DES for threatened abortion in women was responsible for a number of reproductive problems in the offspring ranging from infertility to vaginal adenocarcinoma (*10*).

Investigations in the neonatal rat also indicate that analogs of DDT other than methoxychlor, i.e., 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2,2,2-trichloroethane (*o*,

*Endocrinology/Gerontology Section, Health Effects Research Laboratory, United States Environmental Protection Agency, Research Triangle Park, NC 27711.

p'-DDT), may also have estrogenic activity at the neuroendocrine level. Heinrichs et al. (*11*) found that rats given *o,p'*-DDT as neonates exhibited advanced puberty (vaginal opening), persistent vaginal estrus after a period of normal cycling, follicular cysts, and a reduction in the number of corpora lutea (anovulation). Administration of these compounds to immature or ovariectomized female animals evokes responses in the uterus or oviduct similar to those seen after administration of classical estrogens, such as estradiol (*4*). Based on this assay, methoxychlor and *o,p'*-DDT have been shown to be estrogenic in a number of species (i.e., rat, mouse, mink, quail and chicken) (*4,12*). This effect appears to be directly on the uterine tissue and not through the adrenals, as it is not abolished by adrenalectomy.

DES, chlordecone, methoxychlor, and *o,p'*-DDT analogs also cause adverse reproductive effects in mammalian males. DES has been shown to produce a severe and prompt depression of the adult male rat brain-pituitary-gonadal axis (*13,14*). Chlordecone treatment was reported by Larson et al. (*15*) to cause testicular atrophy in the rat. In man, abnormal sperm counts among industrial workers suffering from chlordecone toxicity have been described (*16*). Hodge et al. (*17*) found reductions in testicular size in rats pair-fed a diet containing 1% technical grade methoxychlor. Gray et al. (*9*) treated male rats with methoxychlor from 21 through 80 days of age and found decreased reproductive performance and altered endocrine parameters in those animals receiving 100 and 200 mg/kg/day. Technical grade DDT was also reported to cause occasional testicular atropy in the rat (*18*), while Krause et al. (*19*) reported damaged spermatogenesis and diminished numbers of Leydig cells in rats given 200 mg/kg DDT from the 4th to 23rd day of life.

The mechanisms by which these estrogenic compounds act to disrupt gonadal function remain unclear. Bulger and Kupfer (*4*) argue that some of the antigonadal effect of DDT and methoxychlor may be directly at the level of the testes. Concentrations as low as 0.4 μM *o,p'*-DDT and 0.1 μM of the active monophenol methoxychlor derivative, HPTE [2,2-bis(*p*-hydroxyphenyl)-1,1,1-trichloroethane], caused a competitive inhibition of the binding of tritiated estradiol to testicular estrogen binding protein (presumably an estrogen receptor). Purified methoxychlor and *p,p'*-DDT [1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethane] had no effect on the estrogen binding protein. These results suggested that HPTE and *o,p'*-DDT could possibly influence androgen formation by acting on testicular estrogen receptors.

The toxic effect of DDT analogs on the male reproductive system might also be mediated through the covalent binding of highly reactive metabolites to macromolecules essential for androgen activity. Bulger and Kupfer (*4*) present evidence that DDT analog metabolites do bind to microsomal components *in vitro*. If metabolites such as these are generated *in vivo* and are able to reach male sex accessory tissue, they could then diminish androgen production by binding to essential components of androgen-secreting cells. Such highly active metabolites could also cause a more generalized destruction of male reproductive tissue.

It is also well known that DDT analogs are potent inducers of hepatic microsomal monooxygenase activity *in vivo* (*4*). Induction of this activity by treatment with DDT analogs could possibly cause a decrease in testicular androgen as a result of enhanced degradation of endogenous androgens by the monooxygenase system.

Although these observations are suggestive, the question remains as to whether these are pharmacological or physiological effects. The effect of DES on male reproductive function could be mediated by a direct action of this estrogenic compound on the hypothalamus and pituitary, tissues that are rich in estrogen receptors (*20*). Incubation of the testis with concentrations of DES that affect reproductive function when administered *in vivo* can be without effect on testosterone secretion (*21*). By measuring a number of endocrine and morphological changes following DES treatment, we found that pituitary LH, FSH, and prolactin concentrations and serum prolactin levels were altered significantly at doses too low to induce any change in testicular weight, serum testosterone, androgen binding protein or testicular morphology (*14,22*). We also found that these changes in pituitary hormone content and secretion occurred sooner after the initiation of treatment than any noticeable change in testicular function (*22,23,*). These data would argue that the pituitary or hypothalamic-pituitary tissue is a primary target for the toxic effects of low doses of estrogenic compounds on the reproductive system. At higher doses, these compounds may affect both the hypothalamic-pituitary axis and the gonads directly. An initial estrogenic effect on the hypothalamus and pituitary was also noted in a study using methoxychlor (*24,25*). Doses of methoxychlor that had no detectable effect on testicular function or reproductive performance in the male rat (25 and 50 mg/kg/day) produced a small elevation in serum prolactin and a large increase in pituitary prolactin concentration. Using an *in vitro* perifusion system, a significant dose-related increase in prolactin release from pituitaries obtained from treated animals was also observed.

Curiously, methoxychlor and DES were found to have opposite effects on pituitary weight (*24*). Although both compounds enhanced pituitary prolactin concentration and prolactin release, raising the dose of DES caused a progressive increase in pituitary weight. Methoxychlor, on the other hand, resulted in a significant decrease in pituitary weight (*25,26*). This would indicate that these two estrogenic compounds are having a differential effect on the pituitary and/or hypothalamic-pituitary axis. Another unexpected finding in pituitary hormonal function was reported by Huang and Nelson (*27*). These investigators studied the effect of chlordecone on LH secretion in response to GnRH in cultured pituitary cells. They found that chlordecone affected LH release in a manner opposite to that observed with es-

tradiol, suggesting that in the pituitary chlordecone acts as an antiestrogen.

Other xenobiotics reported to have estrogenic effects upon the uterus include the polychlorinated biphenyls (*28*), the antidiabetic compound tolbutamide (*29*), and two cathartics, phenolphthalein and phenophthalol (*28*). The cyclosiloxanes (used in various applications, including cosmetics) have also been found to possess estrogenic properties. Cyclosiloxane caused female rats to remain in metestrus or diestrus for the duration of treatment (*30*). Pregnant rats treated before implantation with cyclosiloxane failed to demonstrate ova implantation. LeVier and Jankowiak (*31*) found that treatment of mature males with organosiloxane (33 mg/kg for 7 days) diminished ventral prostate and seminal vesicle weights. Treatment with 10 mg/kg/day for 7 days caused a significant decrease in serum testosterone values. Other findings following cyclosiloxane administration (as low as 0.1 mg/kg/day), were pituitary enlargement and an increase in pituitary prolactin, LH, and FSH.

In summary, there are a number of environmental compounds that possess estrogenic activity. For those that have been evaluated in more detail, it appears that significant changes in pituitary function do occur following treatment and that such changes are involved in the alteration of reproductive function. It is possible that with low doses this effect on the pituitary may be the sole (or at least primary) mechanism responsible for altered reproductive capacity. However, at higher doses a commensurate, direct testicular effect may be involved.

Therapeutic Drugs and Drugs of Abuse

Many classes of drugs exert an inhibitory action on pituitary function. For the most part, these drugs modify hypothalamic control of pituitary hormone secretion by altering CNS neurotransmitter and neuropeptide activity. Consequently, these changes in LH, FSH, and prolactin secretion result in adverse side effects on the reproductive system, including changes in libido, impaired gonadal function, and loss of fertility.

The effects of various therapeutic agents on reproductive function are well known. These drugs may either depress CNS activity (i.e., anesthetics, analgesics, and tranquilizers) or stimulate it (i.e., antidepressants and hallucinogens). In fact, a variety of such agents are often used to probe the central control of neuroendocrine function.

There is ample evidence that certain drugs of abuse alter reproductive function. For example, it has been shown that in rats and mice Δ-9-tetrahydrocannabinol (Δ-9-THC), the major psychoactive component of marijuana, significantly reduces LH, FSH, prolactin, and testosterone concentrations in the blood and causes decrements in sexual organ weights (*32,33*). Correspondingly, studies in the rhesus monkey have shown that a single injection of Δ-9-THC produces a long-lasting depression in gonadotropin levels (*34*). In humans, similar reports of decreased testosterone levels and significant changes in sperm count and morphology have been reported, although there is not general agreement in this regard.

In the female rat, Δ-9-THC has been shown to suppress serum gonadotropin secretion (*35*) and abolish estrous cyclicity (*36*). Δ-9-THC was also found to retard sexual development, as evidenced by a delayed appearance of estrus and ovulation when daily treatment was initiated at 27 days of age (*37*). This alteration in puberty may reflect the depressed levels of serum prolactin present in Δ-9-THC-treated females (*38*), as prolactin is critical for normal pubertal development (*39*). Δ-9-THC has also been found to disrupt ovulatory function in primates (*40*).

The influence of Δ-9-THC on pituitary function is likely mediated through this compound's action on the CNS. The decrease in serum gonadotropins and testosterone levels, following acute Δ-9-THC treatment, can be reversed by treatment with either human chorionic gonadotropin (hCG) or gonadotropin releasing hormone (GnRH) (*41*). Similarly, Hughes et al. (*38*) reported that the fall in prolactin secretion observed after Δ-9-THC treatment *in vivo* was not seen when the pituitary was exposed to Δ-9-THC *in vitro*. However, it has not been determined whether prolonged treatment with Δ-9-THC *in vivo* would result in modified pituitary hormone concentration or release, or whether such changes are reversible.

The opiates also appear to exert their primary effect on the hypothalamic-pituitary axis. Such changes in central regulation of the neuroendocrine axis result in dysfunction of the gonads and sex accessory organs in both man and animals. Clinical manifestations, such as decreased sexual desire and performance, menstrual irregularities and infertility, and increased fetal loss among narcotic users are attributed to altered gonadal functions (*41*). In laboratory animals, significant alterations in pituitary and gonadal functions have been reported, along with functional and structural changes in the integrity of the secondary organs, primarily the seminal vesicles and prostate gland (*42*).

The endogenous brain opioids have been shown to be highly concentrated in the hypothalamus and closely associated with aminergic neurons and those containing GnRH, as well as with steroid-concentrating neurons (*43*). Meites et al. (*44*) reported that a single injection of 2, 10, or 15 mg morphine sulfate caused a decrease in LH levels without changing serum FSH. Similarly, a single injection of met^5-enkephalin also decreased serum LH, but not FSH. In both instances, naloxone reversed this opiate's effect. It is also significant to note that treatment with naloxone alone caused an increase in serum LH and FSH.

In early reports, morphine administration was shown to block LH release and ovulation during the rat's estrous cycle, and this action could be reversed by concomitant administration of naloxone (*45*). In a more recent study (*46*) morphine was infused IV at 1400 hr on

proestrus. Morphine delayed the rise in serum LH by approximately 2 hr and lowered the peak LH values as compared with saline-injected controls. This inhibitory effect of morphine on LH release again was completely reversed by administration of naloxone. Naloxone alone did not alter the peak of the LH surge, but maintained significantly higher serum LH levels than controls during the subsequent decline of this hormone. Neither morphine nor naloxone altered the pattern of the FSH surge, but naloxone completely inhibited the prolactin surge.

Kumar et al. (*47*) observed that both the hypothalamic and pituitary content of the endogenous opioid met^5-enkephalin was very high on the morning of proestrus in rats, but decreased significantly that afternoon and on estrous day. They speculated that the fall in met^5-enkephalin on the afternoon of proestrus may contribute to the surge of LH and FSH, whereas the high levels of the opioid on the morning of proestrus were involved in the rise of prolactin.

Sylvester et al. (*48*) evaluated pituitary function in ovariectomized females treated with estrogen and progesterone. Morphine completely inhibited the LH and FSH surges on the day of drug treatment, but on the following day, a large rebound was observed. In contrast, naloxone administration caused a significantly greater surge of LH and FSH on the day of drug treatment, while completely suppressing such surges on the following day. This difference on the second day did not appear to be due to differences in pituitary gonadotropin concentrations, because treated and control groups released as much hormone in response to GnRH. In long-term ovariectomized rats, morphine decreased the height of the pulsatile LH release and the frequency of the pulses. Naloxone increased the pulse height, but had no effect on pulse frequency (*44*).

In narcotic addicts, testosterone and LH levels are markedly depressed (*49,50*). According to clinical reports, heroin addicts experience both diminished sexual drive and impaired sexual function. Sperm count and sperm motility are also decreased. The exact mechanism by which narcotics suppress sexual function is unknown. The endorphins may have a role in influencing sexual behavior, but it is also likely that decreased testosterone levels are responsible for the lowered libido. It is clear that the narcotic drugs can suppress gonadotropin secretion and stimulate the secretion of prolactin. Both of these effects are likely to be inhibitory to male sexual function (*51*).

Metals

The metal cations represent another class of environmental compounds known to alter reproductive capacity, although the effect that these cations have on pituitary function remains to be determined. Since certain metal ions affect CNS neurotransmitter activity (*52,53*) and accumulate in the pituitary following injection (*54*), it becomes apparent that altered pituitary function could contribute to the toxic effects observed on the reproductive system. Below, we discuss the data available on three of the heavy metals and their possible influences upon pituitary function.

Cadmium

Single subcutaneous injections of 1 or 5 mg cadmium chloride to adult male rats cause a significant reduction in the weights of the testis, epididymidis, vas deferens, ventral prostrate, and seminal vesicles (*55,56*) as well as a decrease in hCG-stimulated testosterone secretion (*57*). Sperm population in the vas deferens, caput and cauda epididymidis were severely reduced. Sexual drive and fertility were unaltered 7 or 15 days after treatment with 1 mg cadmium chloride. However, there was a decrease in sexual activity ranging from altered behavioral activity to total sterility in animals receiving 5 mg. Circulating testosterone and 5 α-dihydrotestosterone were suppressed, whereas androstenedione concentration remained unaltered (*56*). It appears that cadmium chloride not only affects spermatogenesis, but also inhibits androgen production.

The marked necrosis in the testis which follows treatment with cadmium salts probably results from a severe reduction in testicular blood flow and an increase in permeability of the blood vessels and the blood-testis barrier (*58*). In rats, pituitary LH and FSH secretion are also affected. Allanson and Deanesly (*59*) reported "castration-like" changes in the gonadotrophs during the period of testicular necrosis. Similarly, Gray et al. (*60*) reported increased serum FSH levels in male rats treated with a single injection of cadmium chloride between 49 and 70 days of age and sacrificed at 9 months of age. Such observations would indicate that cadmium has its primary effect on the testis and that changes in LH and FSH secretion occur as a result of altered feedback emanating from the damaged testes.

In female mice and rats, cadmium has been reported to cause fetal resorption and malformations (*61*). In the female hamster, cadmium chloride was reported to block ovulation and produce prolonged alterations in ovarian cyclicity (*62*). Whether these effects are a consequence of altered pituitary or ovarian function is unclear. However, cadmium chloride injections near the time of the preovulatory LH surge were more disruptive to subsequent ovarian cycles than those given during other stages of the estrous cycle, indicating that pituitary hormone secretion may have been altered.

Nickel

Adverse effects of nickel on reproductive processes have been reported in rats after the administration of soluble nickel salts. Hoey (*63*) studied the acute and chronic influence on rat testes of nickel sulfate given subcutaneously at 0.04 mmole/kg. At 18 hr after a single dose, shrinkage of central tubules, hyperemia of intertubular capillaries, and disintegration of spermatozoa were observed. The effects of multiple doses were an extension of the acute effects and included further

shrinkage of tubules, disintegration of spermatocytes and spermatids, and cytotoxic effects on Sertoli cells. The changes were reported to be nearly completely reversible. Inhibition of spermatogenesis has also been observed after daily oral administration of nickel sulfate at 25 mg/kg. Reductions in the number of basal cells within the tubules and in the number of tubules that contained spermatozoa were reported. Male rats given nickel sulfate at 25 mg/kg for 120 days were apparently infertile, inasmuch as no pregnancies resulted when the males were caged with females in estrus.

In the rabbit, Parker and Sunderman (*54*) found that of the various tissues studied, the concentrations of nickel in the pituitary were second only to those in the kidneys. This observation was independently confirmed by Clary (*64*) in his investigation of the distribution of nickel in guinea pig and rat tissues. The finding that nickel is heavily localized in the pituitary may have physiologic significance. Clemons and Garcia (*65*) found that a single subcutaneous injection of nickel chloride (10 and 20 mg/kg) in the rat led to a profound and consistent increase of circulating prolactin after one day which lasted for four additional days. There was also an elevation in insulin levels that appeared 1 and 2 days post-injection. The nickel-induced prolactin rise could be abolished by a simultaneous administration of the dopamine receptor blocker, CB154. *In vitro* incubation of pituitaries from rats that received 20 mg/kg nickel 48 hr prior to sacrifice released more prolactin into the culture medium and contained more prolactin in the final tissue homogenate than did pituitaries from control animals. Also, the hypothalamic extracts obtained from nickel-injected rats were tested *in vitro* with normal rat pituitaries in an effort to evaluate their ability to inhibit prolactin secretion. The hypothalamic extracts obtained from treated animals possessed less prolactin-inhibiting ability (dopamine concentration?) than the extracts obtained from control rats. The results show that nickel chloride has effects on the endocrine system that last considerably longer than previously reported. These data also demonstrate that the influence of nickel chloride upon the reproductive system may be mediated through the neuroendocrine changes and, instead of specifically inhibiting prolactin secretion from the pituitary as previously reported in short-term studies (*66,67*), nickel chloride promotes high circulating prolactin levels lasting 1 to 4 days.

The fact that nickel, as well as other metal cations, can affect pituitary function through a direct action has been demonstrated in other studies using *in vitro* perifusion techniques. The addition of nickel chloride (50 μM), zinc chloride (50 or 200 μM), or cobalt chloride (100 μM) to the perifusion medium resulted in a dramatic decrease in prolactin release (*68–70*). These observations demonstrate a direct effect of the metal ions on pituitary hormone secretion. Whether or not the concentrations of the metal ions used in these studies approximate the concentrations reaching the pituitary following traditional routes of exposure remains to be determined.

Lead

Sokol et al. (*71*) evaluated the effect of lead on reproductive function in order to ascertain what reproductive abnormalities occur in experimental animals exposed to low levels of lead. Fifty-two-day-old male rats were treated with water containing 0.00, 0.1, or 0.3% lead acetate for 30 days prior to killing. Blood lead levels were below detection in the control, 3 μg/dL in the 0.1% and 60 μg/dL in the 0.3% lead acetate group. There was a significant negative correlation between blood lead levels and serum and intratesticular testosterone values. As the level of lead exposure increased, intratesticular sperm counts declined. No changes in serum LH values were found, but sperm and FSH values were significantly suppressed after treatment. There was a decrease in ventral prostate weight, but no differences in testicular or seminal vesicle weights. The authors conclude that exposure to lead resulting in whole blood serum lead values considered acceptable in the workplace (≤ 40 μg/dL) causes inhibition of testicular function. The failure to demonstrate elevated LH and FSH in the face of markedly decreased serum testosterone and ventral prostate weight suggests either a principal mechanism of action of lead toxicity at the level of the hypothalamic-pituitary axis or a combined defect involving the gonad and hypothalamic-pituitary sites.

Autoradiographic studies have localized lead within the median eminence of the hypothalamus (*72*). Lead is known to affect the release of a number of brain neurotransmitters, including norepinephrine and dopamine. Unfortunately, scarce and conflicting data have been reported on the effects of lead on hypothalamic neurotransmitter concentration and turnover (*73*).

In a clinical study, Braunstein et al. (*74*) reported a blunting of the pituitary response to clomiphene and gonadotropin-releasing hormone in lead-poisoned men. These data further support the possibility that lead toxicity impairs hypothalamic-pituitary function.

Although reports describing the effect of lead on CNS function are inconsistent, a regional analysis of DA function in the rat reveal changes that would be consonant with potential changes in dopaminergic (DA) neurotransmission and pituitary prolactin secretion. Govoni et al. (*75*) evaluated the effect of chronic dietary lead exposure on the brain nigrostriatal, mesolimbic and mesocortical dopaminergic systems. They found no alterations of DA receptors, measured either as dopamine sensitive adenylate cyclase or as (^{3}H)-spiroperidol binding. On the other hand, dopamine synthesis appeared to be reduced in the striatum, unaffected in the substantia nigra and increased in the nucleus accumbens and frontal cortex. The increase of DA synthesis observed in the accumbens would be consistent with the hyperactive behavior that has been reported following lead intoxication. The effect of lead exposure on the hypothalamic DA mechanisms regulating prolactin secretion were also studied in rats by measuring the concentration of DA and its metabolite DOPAC (dihydroxyphenylacetic acid) in the hypothalamus,

along with DA receptor densities in the hypothalamus and pituitary (*76*). Decrements in hypothalamic DOPAC concentrations and DA receptor density in the pituitary were found. The decreased DA binding in the pituitary is consistent with the elevated serum prolactin concentrations described in lead-exposed rats (*77*). These authors argue that decreased DOPAC with normal levels of DA indicates a lowered DA "tone" in the hypothalamus. They further argue that pituitary DA receptors become "subsensitive" in spite of lower hypothalamic DA levels and that the interference by lead with the central neuroendocrine processes may contribute to the delayed sexual development and decreased reproductive ability observed during lead intoxication.

Lead has also been reported to alter thyroid function, and this could affect pituitary regulation of the gonads. Bruni et al. (*78*) noted that hypothyroid humans, monkeys, rats, and mice were deficient in gonadotropins and had irregular or no menstrual and estrous cycles. Thyroidectomy of male and female rats with intact gonads results in a significant decrease in serum LH and FSH, as well as a decrease in serum testosterone in the male. Administration of a replacement dose of thyroxine (T_4, 2,5 μg/100 g body weight) elevated serum LH and FSH in the females to the level of control, intact values, and returned serum LH and testosterone to the level of control males. Since thyroid function is apparently important for normal pubertal development in the male, the effects of thyroidectomy and treatment with thyroxine were studied in immature male rats by Chowdhury et al. (*79*). Thyroidectomy was found to inhibit gametogenesis and Leydig cell development. However, the effects could be reversed with administration of 10 μg T_4 (injected intraperitoneally daily for 30 days).

In humans, Robins et al. (*80*) found low values for serum thyroxine and estimated free thyroxine in 7 of 12 workers referred because of elevated blood lead levels. They concluded that there is a substantial inverse relationship between blood lead and serum thyroxine. This could be overcome with TRH or TSH. Such observations would be compatible with a central depression of the thyroid axis, or an alteration in thyroxine metabolism or binding to proteins.

Other occupational and environmental agents have been noted to cause depressed thyroid function, including the polybrominated biphenyls and carbon disulfide. Polybrominated biphenyls are associated with an antithyroid and antibody-positive primary hypothyroidism (*81*). In workers exposed to carbon disulfide, low T_4 values were present in 40% of the individuals tested (*82*). In neonatal rats, chlorine dioxide has been reported to depress thyroid function (*83*), and this compound, which has been suggested as an alternative to chlorine for drinking water disinfection, has been implicated as a potential antithyroid agent in the monkey (*84*). In female mice, treatment with the herbicide, 2,4-dichlorophenyl-*p*-nitrophenyl ether (nitrofen) for 3 days caused a dose-related reduction in serum thyroxine levels, although triiodothyronine (T_3) was not affected (*85*). The importance of these changes in thyroid function to the reproductive axis remains to be explored.

Finally, lead may also have a direct testicular effect. Wiebe et al. (*86*) isolated Sertoli cells from the testes of prepubertal rats and cultured them in the presence of 2.64×10^{-4} M of lead acetate for 1, 4, 24, 48, 96, and 144 hr. They found no reduction of FSH binding or FSH-induced cyclic AMP after 1–4 hr exposure to lead. After 24 hr exposure to lead acetate the Sertoli cells exhibited a 10–20% decrease in FSH binding and cyclic AMP production, and after 96 hr there was a 75% decrease in these two parameters. After *in vitro* exposure to lead acetate for 48 hr, the steroidogenic activity (progesterone conversion to steroid metabolites) of the Sertoli cells was significantly reduced and steroidogenesis was no longer stimulated by FSH.

Summary

A variety of environmental compounds are known to have deleterious effects on reproductive function. The effect that estrogenic compounds and narcotics have on pituitary function is well documented. The majority of studies have shown that these substances alter reproductive capacity through their direct action on the pituitary or alter pituitary function through their action on neural tissue. In contrast, the extent to which industrial byproducts and other classes of xenobiotics affect pituitary function is unknown. This lack of information is unfortunate, because changes in pituitary hormone secretion may prove to be a sensitive index useful in determining the potential toxic effect that certain classes of compounds possess. Additionally, since the neuroendocrine control of pituitary hormone secretion is well understood, these measures can provide useful information concerning the mechanisms through which certain compounds alter reproductive capacity.

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