Blood urea and fertility in dairy cows and humans: Possible mechanisms and sites of action

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Introduction

The purpose of this paper is to highlight some insights concerning the impact of increased blood urea concentrations on reproductive functions in dairy cows, humans and experimental animals. In ruminants such as cattle, sheep and goats the main source of high level of urea in blood is a diet with an excess of nitrogenic compounds. Urea produced by the liver enters the blood circulation. From there, it can be excreted in urine, recycled into rumen or absorbed by the mammary gland. In humans and experimental animals such as rats, urea is a metabolic waste product, which is excreted at a constant rate via the kidney. High levels of urea in the blood indicate a problem with the removal or over-production of urea in the body due to metabolic and others disorders. The most common cause of uremia in humans is kidney failure such as chronic renal insufficiency (CRI). A great effort has been seen during the last three decades to understand the mechanism by which a high protein diet and urea impair fertility in dairy cows. But not all studies have confirmed the relationship between blood urea and fertility and some showed conflicting results. Considerable variations might be caused by modifying factors such as parity, health status, season, feeding pattern, age, order of lactation, degradability of protein and energy intake (1,2,3,4,5). Dietary insufficiencies may affect any of three organs: hypothalamus, pituitary and ovary (5). Dietary insufficiencies may affect any of three organs: hypothalamus, pituitary and ovary (5).

Toxic effect of increased urea and ammonia

When the concentration of ammonia exceeds the detoxication capacity of the liver, concentrations of ammonia rise throughout the body and may exert toxic effects on mammalian cells (6). The hypothesis suggests that high ammonia and urea concentrations impair fertility through a direct toxic effect on sperm, ovum, implantation and embryo development (Sinclair et al. 2000, Mc Evoy et al 1997). Sites of a potential direct effect of urea or ammonia include the oviducts, uterus and hypothalamic-pituitary- gonad axis. High plasma urea or ammonia levels can change the uterine environment, (7), but the mechanism by which pH gradient may affect fertility is not known (8). The increased pH gradient in the uterine environment may alter composition of the uterine secretion (9) and thus reduce embryo development (10). In in vitro studies of bovine cell culture, Butler (11) showed that urea altered both the pH gradient across the cells and increased secretion of prostaglandin F2α that may interfere with embryo development. Increased plasma urea levels might interfere with normal inductive actions of progesterone in the microenvironment of the uterus, thereby causing suboptimal conditions for the support of embryo development (12).

One proposed mechanism suggests that high plasma urea or ammonia concentration may reduce LH binding to ovarian receptors, resulting in reduced ovulation rate and decreased progesterone production (7). McEnvoy et al (9) concluded that dietary excess of urea could influence the viability and metabolism of embryo in ewes and alter rates of fetal development. They found that this detrimental effect on embryo was not mediated through alternations in preovulatory endocrine activity but due to the toxic effects of elevated levels of ammonia. However, Daschler et al (13), in study with uremic rats, concluded that inhibition of GnRH secretion by uremic serum specifically acts at the hypothalamus and did not result from a general cytotoxicity of uremia. If this is true, than secretion of GnRH in the hypothalamus is not altered by the toxic effect of urea, but other mechanisms are involved. This conclusion supports the need for further research to elucidate mechanism by which urea acts in hypothalamo-pituitary axis on GnRH/LH secretion and which possible neurotransmitters and sites are involved in this mechanism.

Imbalance in protein and energy supply (not reviewed in this paper)

An imbalance between protein and energy intake may affect the efficiency of metabolism, rumen functions and contribute to increased ammonia (or) urea in portal blood. There is growing support for a mechanism which does not implicate the direct effects of plasma urea or ammonia on fertility in cows on high protein intake. An interaction between protein and energy intake and excessive energy losses due to conversion of plasma ammonia to urea was considered in some studies (14,15).

Urea alters GnRH/LH secretion

It is well documented that high serum urea may alter GnRH /LH secretion in humans and experimental animals with chronic renal insufficiency (CRI). These findings lead to the prediction that excess urea may interfere with the neuromodulation of episodic GnRH/LH release in cows, especially during the early post-partum period. Jordan and Swanson (16) found an exaggerated response of the pituitary to GnRH injection and increased basal LH in serum of cows fed high level of crude protein. These results indicate that high protein intake, and consequently increased serum urea, may increase responsiveness of the pituitary to GnRH, resulting in impaired fertility. Lactating cows seem to be more sensitive to high urea levels in a negative energy balance than non-lactating cows on a maintained energy intake (17). This is in accordance with Blaukwiekel et al. (18) who did not confirm a primary effect of urea on LH or progesterone concentration in nonlactating cows. High levels of serum urea and ammonia did not affect the timing or level of LH release during preovulatory surge in study of Sinclair et al. (17). In contrast, Krieg et al. (19) reported a significant decrease in the preovulatory LH surge in female rats in experimental uremia. Ovulation and the preovulatory LH surge were depressed significantly despite mild elevation in urea. To date, the influence of plasma urea on hypothalamic-pituitary functions in dairy cows is not entirely known.
Experimental uremia induced by subtotal nefrectomy in mature rats causes gonadal dysfunction, which is principally due to aberrant neuroendocrine regulation of GnRH secretion involving inhibition of GnRH secretion, hypersensitivity to negative testicular

feedback, and resistance to naloxone cit. Handelsman, Dong (20). Veldhuis et al.(21) investigated the nature of putative disturbance in pulsatile LH secretion in men with CRI. They concluded that uremia was accompanied by a specific defect in the pulsatile mode of LH secretion, resulting in abbreviation of LH secretory burst duration and consequent fall in mass of LH secreted per spontaneous release episode. Dong and Handelsman (22) investigated the effect of experimental uremia on LH secretion in castrated rats. They found that uremia caused decreased LH pulse frequency independent of testicular feedback, increased LH pulse amplitude (157%) and increased mean LH levels (335%) compared to control rats. This paradoxical LH hyper-elevation, after castration, was linked to pituitary hypersensitivity to GnRH. In another study Dong, Handelsman (20) characterized the nature of the defect in the hypothalamic opiatergic mechanism in experimental uremia in rats. They suggested that uremia might decrease the release of endogenous opioid peptides that interact with GnRH neurons from medial basal hypothalamus. Direct sampling of hypothalamus-pituitary portal blood in uremic rats has confirmed GnRH deficiency (24). However, it was not clear whether reduced hypothalamic GnRH release was due to the imbalance of local excitatory and inhibitory neuronal afferences in the hypothalamus, or to a direct effect of uremia on neurosecretory cells that constitute the GnRH pulse generator.
In an *in vivo* study in rats, using intracerebral microdialysis, Schaefer et al.2001 (25) examined the amino acid neurotransmitter milieu in the preoptic area (POA) of the hypothalamus where the GnRH neurons reside. Both neuroinhibitory and neuroexcitatory amino acids (EAA) in POA of rats with CRI were observed. These authors suggested that reduced GnRH secretion in experimental renal failure was due to increased inhibitory GABA tone that outweighed the concomitant elevation in EAA. Daschner et al. (13) in a *vitro study* suggested that uremic serum contains macromolecular and hydrophilic peptides able to specifically suppress the neurosecretion of GnRH from GT 1-7 cells.

Conclusion

The present review demonstrates that increased urea or ammonia in blood is linked to impaired in fertility in cows and humans. Although more research is needed to elucidate the mechanism by which urea affects GnRH secretion, recent findings allow one to speculate that increased serum urea concentration may: (1) alter the environment of hypothalamus (2) exert a direct (toxic) effect on neurosecretory cells that constitute GnRH pulse generator (3) alter the amino acid neurotransmitter milieu in the POA, and thus contribute to the impaired function of GnRH pulse generator (4) decrease the release of endogenous opioid peptides that interact with GnRH neurons in the medial basal hypothalamus.
In cows, possible sites of urea impact include: hypothalamo-pituitary-ovarian axis, gametes, embryos in the oviduct and uterus and some metabolic hormones, such as insulin and immune system. Several hypothesis have been proposed: (1) direct toxic effect of urea or ammonia on sperm, ovum, implantation and embryo development, in uterus (2) increase the pH gradient in uterine environment and thus affect uterine secretion and embryo development (3) high serum urea concentration may alter prostaglandin and/or progesterone production that may interfere with embryo development (4) dietary urea excess may reduce LH binding to ovarian receptors resulting in reduced ovulation rate and

decreased progesterone production (5) imbalance between protein and energy intake may affect the efficiency of metabolism and rumen functions, and contribute to the detrimental effect of urea on fertility (6) increased serum urea may interfere with secretion of GnRH/LH, especially during early postpartum.

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