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Opioidergic, adrenergic and GABAergic modulation of growth hormone and cortisol secretion: A review

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ABSTRACT

Growth hormone (GH) and cortisol are the major metabolic hormones having multiple functions controlling almost every organ system of the body in laboratory and domestic animals. Basically, the release of adenohypophyseal growth hormone is regulated positively and negatively by 2 central neurohormones, growth hormone-releasing hormone (GHRH) and somatostatin, respectively. Similarly, the activity of hypothalamo-pituitary-adrenal axis is mainly under the control of hypothalamic corticotrophin-releasing hormone (CRH) and argenine vasopressin which subsequently regulate the adrenocorticotropin hormone (ACTH) from pituitary and cortisol from adrenal gland. In the recent past, literature has revealed the classical hypothalamic regulation of these 2 hormones involving many other neurogenic and humoral factors. These factors involve sequential events acting through opiodergic, adrenergic and GABAergic mechanisms. However, the effect of these neurotransmitters in modulation of GH and cortisol secretion varies with site of action of these neuropeptides and species involved, and is greatly influenced by age, sex and physiological status of an individual.

Key words: Catecholamines, Cortisol, GABA, Growth hormone, Opioids

In domestic animals, the release of adenohypophyseal growth hormone (GH) is modulated positively and negatively by 2 central hypothalamic neurohormones, growth hormone releasing hormone (GHRH) and somatostatin (SS), respectively. The secretion of these neurohormones is further regulated by different central neurotransmitters and neuropeptides (Muller 1987, McMahona *et al.* 2001). The hypothalamic hypophysiotrophic neurons are densely innervated by adrenergic and noradrenergic nerve terminals and proopiomelanocortin (POMC) containing neurons (Al-Damluji, 1993¸ Leshin *et al.* 1988). Additionally, there is ultrashort-loop positive feedback of somatostatin on GH secretion in hypothalamus (Murakami *et al.* 1987a) mediated via hypothalamic GHRH (Murakami *et al.* 1987b) and also ultrashort-loop negative feedback of GHRH on GH secretion (Lumpkin *et al.* 1985).

Similarly, the activity of hypothalamo-pituitary-adrenal (HPA) axis is regulated by corticotrophin-releasing hormone (CRH), argenine vasopressin (AVP) and the glucocorticoid-mediated negative or positive feedback action. The above sequential events in controlling cortisol secretion are mediated by opioidergic, adrenergic and GABAergic mechanisms at brain level (Barb *et al.* 1991, Bugajski *et al.* 1991, McCann and Rettori 1986). Thus, this review describes the role of adrenergic, opioidergic and GABAergic pathways in regulation of growth hormone and cortisol secretion.

Opioidergic modulation of growth hormone

A stimulatory role of opioidergic mechanisms on growth hormone secretion was demonstrated in domestic animals (Trudeau *et al.* 1988, Leshin *et al.* 1990, Parrott and Goode 1992). In rats and heifers, opioid analogs stimulated GH which was suppressed by naloxone pre-treatment (Katakami *et al.* 1981a, Armstrong and Johnson, 1989, Leshin *et al.* 1990) such effects of opioids are mediated via opioid receptors on GHRH and somatostatin neurons (Willoughby *et al.* 1991, Janik *et al.* 1994).

Similarly, endogenous opioids agonist (morphine) transiently increases GH in intact and castrated immature pigs and this increase is delayed when naloxone is given immediately after morphine (Trudeau *et al.* 1988). Naloxone alone does not affect growth hormone secretion in immature male pigs and sexually mature boars (Trudeau *et al.* 1988, Estienne *et al.* 2002) but decreases GH in lactating sows (Armstrong *et al.* 1990). Naloxone also attenuates N-methyl-d, l-aspartate (NMA)-stimulated growth hormone in ovariectomized gilts (Chang *et al*. 1993) but this effect of NMA was not attenuated by naloxone in sheep (Estienne *et*

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al. 1990). Naloxone inhibits stress-induced growth hormone secretion in pre-pubertal gilts but does not influence GH in unstressed pigs (Rushen *et al.* 1993). It implies that naloxone reduces the stimulated growth hormone secretion and does not influence basal secretion which also involves species differences. However, we have observed a dual stimulatory as well as inhibitory effect of opioid antagonists on GH secretion in gonadectomized swine (Phogat and Parvizi, unpublished observations).

The stimulatory effect of endogenous opioids on GH secretion is believed to be mediated by increased hypothalamic GHRH and suppression of somatostatin secretion (Murakami *et al.* 1985, Wehrenberg *et al.* 1985). Such effects of endogenous opioids on hypothalamic GHRH and somatostatin are further mediated via alpha-adrenergic and GABAergic mechanisms (Katakami *et al*. 1981a, Katakami *et al*. 1981b). However, in dogs, this opioid stimulated GH secretion is independent of adrenergic mediation (Casanueva *et al.* 1981) suggesting a species difference. However, a direct effect on pituitary was also suggested via increased somaostatin activity and such effects are modulated by sex and gonadal steroids (Barbarino *et al.* 1987, Villa *et al.* 1997).

Adrenergic modulation of growth hormone

The catecholaminergic pathways play a significant role in control of growth hormone secretion. The hypothalamic hypophysiotrophic neurons are densely innervated by adrenergic and noradrenergic nerve terminals (Al-Damluji 1993) and somatostatin-containing nerve fibers receive neural inputs from adrenergic system (Kakucska and Makara 1983). The alpha-adrenergic mechanisms are stimulatory and beta-adrenergic systems are inhibitory where stimulation of alpha-adrenoceptors stimulates GH release, probably via stimulation of GHRH and inhibition of somatostatin release, while activation of beta-adrenergic receptors inhibits GH release via stimulation of hypothalamic somatostatin (Krieg *et al.* 1988, Al-Damluji 1993).

Alpha-adrenergic agonists enhance GH secretion. An alpha-2 agonist stimulate GH secretion in cattle and sheep (Sartin *et al.* 1991, Soyoola *et al.* 1994), whereas alpha-1 agonist reduces basal and stimulated GH secretion in dogs (Bluet-Pajot *et al.* 1993) suggesting that alpha-adrenergic modulated GH secretion is species dependent. The stimulatory effect of alpha-2 agonists is via GHRH since alpha-2 activation stimulate secretion of GHRH but not somatostatin from hypothalamic tissue *in vitro* (West *et al.* 1997) and antiserum to GHRH pretreatment inhibits the GH response to clonidine in rats (Cella *et al.* 1987). This mechanism may be mediated via serotonergic pathways as alpha-2 adrenoceptors are located on serotonergic neurons which stimulate serotonin and subsequently GHRH release (Aulakh *et al.* 1992). The inhibitory effect of alpha-1 adrenergic receptors is mediated via somatostatin since administration of anti-somatostatin serum completely abolished the inhibitory effect of methoxamine on GH secretion (Cella *et al.* 1987) and injection of alpha-1 adrenoceptor agonist in periventricular nucleus inhibits GH secretion in rats perhaps via increased secretion of somatostatin in hypophysial-portal blood (Willoughby *et al.* 1993).

Similarly, beta-adrenergic receptors also play a significant role in regulation of GH secretion. In rats and non-human primates, beta-agonists inhibit and beta-antagonists augment the basal or GHRH-induced GH secretion (Schaub *et al.* 1980, Huang and McCann 1983, Park *et al*. 2003). Propranolol blocks the nor-adrenaline suppressed plasma growth hormone concentrations in ewes (Thomas *et al.* 1994) and potentiates the GHRH-induced GH secretion in dogs (Regnier *et al.* 1992, Park *et al.* 2003). Propranolol treatment also increased basal GH secretion in swine (Phogat and Parvizi, unpublished observations). Similarly, GHRH-induced GH response is enhanced by beta-1 adrenergic antagonist (atenolol) but is inhibited by beta-2 adrenergic agonist (salbutamol) in women (Gianotti *et al.* 1998). The lack of beta-adrenergic blockade of GHRH-induced GH release in pituitary grafted rats suggested that the effect of beta-adrenergic blockade on GHRH-induced GH secretion is mediated by an effect on the hypothalamus (Krieg *et al.* 1989) by inhibiting hypothalamic somatostatin release as confirmed by *in vitro* studies in male rats (Richardson and Twente 1990). However, propranolol did not influence the growth hormone-releasing peptide-2 (GHRP-2)-induced GH secretion in ovariectomized ewes (Roh *et al.* 1997). Similary, pulsatile or basal secretion of GH is not altered by beta-antagonist in rats and dogs (Regnier *et al.* 1992, Chapman *et al.* 1993).

There is ample evidence to suggest the mediating role of somatostatin in beta-adrenergic-regulated GH secretion. Beta adrenergic activation reduced GH response to GHRH which was prevented by pretreatment with somatostatin anti-serum suggesting role of somatostatin at pituitary level (Krieg *et al.* 1988, Ghigo *et al.* 1990). Isoproterenol also increased portal venous level of somatostatin (Bluet-Pajot *et al.* 1993). Contrarily, isoproterenol stimulates basal and GHRH-stimulated GH release and its synthesis in rat and ovine pituitaries *in vitro*, and such effects are gonadal steroid-dependent (Evans *et al.* 1985, Soyoola *et al.* 1994) suggesting a direct effect on pituitary.

GABAergic modulation of GH secretion

In general, GABA has got a stimulatory effect on GH secretion. Intravenous or intracerebroventricular administration of GABA stimulates growth hormone secretion in rats and sheep (Murakami *et al.* 1985, Spencer *et al.* 1994). Dietary supplementation of GABA also increases growth hormone concentrations in rats (Tujioka *et al.* 2009).

This increase in GH in response to GABA is due to

increased secretion of hypothalamic GHRH (Murakami *et al*. 1985) and decreased secretion of somatostatin as suggested in rats (Willoughby *et al.* 1986). However, in sheep GABA-induced secretion of GH is independent of somatostatin (Spencer *et al.* 1994). However, a direct stimulatory effect of GABA/agonists on pituitary in modulation GH was reported (Acs *et al.* 1987). Synthesis of GABA in the pituitary and presence of GABA receptors in rat pituitary gland suggests an autocrine role of GABA in regulation of GH at pituitary (Gamel-Didelon *et al.* 2002). A sexual dimorphic (Monteleone 1988) and role of gonadal steroids (Orio *et al.* 2001) in GABA-modulated GH secretion was also suggested.

An inhibitory effect of GABA on GH secretion also exists. The intravenous administration of GABA abruptly increases GH but when given i.c.v. in small doses, it increases the GH but higher doses decreases GH in sheep suggesting dual sites of GABA action in controlling GH release (Spencer *et al.* 1994). Additionally, exercise-induced increase in GH secretion was also reduced by GABAergic agonist (Coiro *et al.* 1994).

Other neurotransmitters also have interaction with GABA in modulation of GH secretion at hypothalamus where the stimulatory effect via GHRH is mediated by excitatory amino acids (Aguilar *et al*. 2005) and inhibitory effect of somatostatin is mediated via alpha adrenergic mechanisms and not by opioid mechanism (Murakami *et al.* 1987a). However, in men, exercise-induced increase in GH secretion was completely abolished when naloxone was given in combination with sodium valproate suggesting an opioid modulation of GABAergic inhibitory action (Coiro *et al.* 1994). Recently, we have found that the inhibitory effect of beta-adrenergic system on GH secretion in swine which is partially mediated via endogenous opioids and the stimulatory effect of GABA on GH release is potentiated and prolonged when endogenous opioids are blocked by naltrexone (Phogat and Parviz, unpublished observation).

Opioidergic modulation of cortisol secretion

In general opioids have been reported to suppress cortisol secretion in different species. Opioidergic antagonist naloxone increases basal ACTH/cortisol secretion in male and female pigs (Estienne *et al.* 1988, Phogat and Parvizi 2007) and dairy cows (Rushen *et al*. 1999). Opioid antagonists also increases cortisol secretion in pre-pubertal gilts (Rushen *et al.* 1993) and gonadectomized male pigs (Phogat and Parvizi 2007) when gonadal steroids are at low level. However, naloxone inhibits cortisol in lactating sows (Barb *et al*. 1991) suggesting a role of underlying physiological environment in opioid-modulated cortisol secretion. Effect of naloxone on cortisol secretion is also gender specific; effects being stronger in females than males (Uhart *et al.* 2006). Such effects of naloxone on ACTH and cortisol response are through adrenergic receptors (Al-Damluji *et al.* 1990).

Naloxone treatment also increases the ACTH and cortisol response to acute stress of nose-sling in pigs (Janssens *et al.* 1995, Phogat and Parvizi 2007) and cortisol response to handling in sheep (Parrott and Thornton 1989). Morphine (iv) pretreatment reduced icv CRH-induced cortisol secretion in sheep (Parrott and Goode 1992).

Adrenergic control of cortisol secretion

It is well established that many stimuli that activate the sympathetic-adrenomedullary system to stimulate epinephrine and nor-epinephrine secretion also activate the pituitary adrenocortical axis (Axelrod and Reisine 1984, Koopmans *et al.* 2005). Such effects on HPA are mediated via alpha and beta-adrenergic receptors centrally (Axelrod and Reisine 1984, Tilders *et al.* 1986) as no direct effect of propranolol was observed on pituitary (Bugajski *et al.* 1991). Similarly, noradrenaline or adrenaline–induced corticosterone in rats is mediated by both alpha and beta adrenergic receptors by acting at a supra-pituitary level (Bugajski *et al.* 1991). Adrenergic and noradrenergic nerve fibres from the brain stem terminates in paraventricular nucleus, the site of cell bodies of CRH neurons (Al-Damluji 1988). In rats, immunocytochemistry studies also suggest that adrenergic neurons lie in close proximity to CRF cell bodies in the paraventricular nucleus (Mezey *et al.* 1984), but noradrenergic terminals are in close contact with CRH and AVP cell bodies in paraventricular nucleus in sheep (Ghuman *et al.* 2010). However, epinephrine-induced cortisol secretion in bovine adrenocortical cells was completely blocked by propranolol suggesting a direct effect on adrenal as well (Ehrhart-Bornstein *et al.* 1998). Such effects of beta-receptors on cortisol secretion are ovarian steroid dependent and are also influenced by stage of oestrus cycle (Petrovic *et al.* 1985).

Propranolol treatment increases plasma ACTH and cortisol (Simeckova *et al*. 2000). Beta blockade with propranolol also augments ACTH and cortisol secretion in response to stress and exercise (Oberbeck *et al.* 1998, Viru *et al.* 2007) but in pigs propranolol did not alter cortisol response to exercise but decreased cortisol response to acute stress (Weiss *et al.* 1974, Phogat and Parvizi 2007) suggesting a species difference in adrenergic regulation of cortisol secretion. Contrary, in healthy man, propranolol decreases the CRH-induced ACTH secretion but increases the cortisol (Kizildere *et al.* 2003).

Beta-agonist isoproterenol also increased basal ACTH/cortisol secretion in male and female pigs and rats (Maunders *et al.* 1987, Bugajski *et al.* 1999, Phogat and Parvizi 2007) but not in man (Al-Damluji *et al.* 1988). However, recently we have not observed any effect of either beta-agonists or antagonists on basal cortisol secretion in immature pigs (Phogat and Parvizi, unpublished observation).

GABAergic modulation of cortisol secretion

GABA has an inhibitory influence on HPA axis (McCann and Rettori 1986). Alprazolam (a benzodiazepine activating GABA-A receptor agonist) inhibits the spontaneous and stimulated HPA axis activity in animals (Kalogeras *et al.* 1990) by inhibiting CRH secretion from hypothalamus (Joyner *et al.* 1998). Alprazolam also suppressed both expression and secretion of CRH from hypothalamus but not CRH-stimulated ACTH/cortisol in rats (Kalogeras *et al.* 1990, Grottoli *et al.* 2002). Parvocellular subdivisions of the PVN are densely innervated with inhibitory GABAergic and excitatory glutamatergic afferents (van den Pol 1991). In sheep, GABA terminals are close to CRH and not to AVP cell bodies in paraventricular nucleus (Ghuman *et al.* 2010). Intracereboventricular administration of GABA lowers concentrations of CRH in portal blood in rats (Plotsky *et al.* 1987) and GABA also inhibits the release of CRH from rat hypothalamic explants *in vitro* (Hillhouse and Milton 1989). However, a direct inhibitory effect of alprazolam on adrenal in mobulation of cortisol secretion was reported (Grotolli *et al.* 2002).

Alprazolam inhibits hypoglycemia-induced HPA and adrenomedullary response in monkey (Van Vugt *et al.* 1997, Giordano *et al.* 2006) and also inhibited exercise or AVP-induced ACTH and cortisol secretion in human beings (Torpy *et al.* 1994, Deustar *et al.* 2005). Octadecaneuropeptide (ODN) which inhibits benzodiazepine binding to the GABA-A receptor lowers plasma cortisol in growing pigs (Parrott *et al.* 2000) but GABA itself did not alter basal cortisol in pigs (Phogat and Parvizi, unpublished observations). The benzodiazepine agonists and antagonists also could not alter CRH-induced cortisol in pigs (Parrott and Vellucci 2000).

An interaction of GABA with other neurotransmitters in modulation of ACTH/cortisol secretion was observed. Alpralozam inhibited naloxone-stimulated cortisol in man (Joyner *et al.* 1998) whereas inhibitory effect of alpralozam on excercised-induced cortisol secretion was decreased by opioid antagonist naloxone (Coiro *et al.* 2011). However, GABA/receptor agonist could not influence opioid/antagonist-induced increase in cortisol in pigs (Phogat and Parvizi, unpublished observations).

It is concluded that adrenergic, opioidergic and GABAergic pathways play a great role in regulation of growth hormone and cortisol secretion by acting both at hypothalamus and pituitary level and these effects are influenced by age, sex, species and physiological state of an individual. The information on inter-relationship of these different neurotransmitters involved in regulatory mechanisms of GH or cortisol secretion are inadequate and further studies are required by using different drug combinations of agonists and antagonists to understand these interactions particularly in domestic animals. This review gives the detailed account of control of secretion of growth hormone at brain level in different domestic animals, however the information in this regard in buffaloes is completely lacking. Thus, this review should help in designing and execution of experiments in different buffalo rearing countries particularly India to understand the regulation of GH in buffaloes to achieve the target of growth and early maturity in this virtuous species.

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