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Review Article

Corticotropin Releasing Factor, Social Stress, and Functional Incontinence in Children

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Abstract

In neurologically normal children with functional urinary incontinence there still are a number of unexplained characteristics: a girls/boys ratio of almost four, the co-existence of bladder and colonic dysfunction, the cure rates obtained with cognitive-behavioral therapy, and the variation of urodynamic patterns over time.

In rodents, experiments with social stress provoke gender specific simultaneous responses of bladder and colon activity, mediated by the corticotropin releasing factor signaling pathway. These responses to social stressors (social instability in females and social defeat in males) provide homologous models for overactive bladder in girls, and Hinman's syndrome in boys.

In school-age children, social stress as a cause of behavioural and emotional problems has been investigated mainly with self-reported questionnaires. Teacher rating scales are a more objective tool to identify behavioural and emotional problems, as well as the social stressors.

To find a link between episodes of incontinence and social stress, we rely too much on parental documentation of incontinence. We need to document incontinence objectively, on a time line of consecutive days and nights, as long as it takes to register at least one episode. 'Wearable electronics' can do this: underwear with woven-in sensors for humidity/temperature, connected to a data-logger.

Keywords: *Corticotropin Releasing Factor; Social Stress; Functional Incontinence; Children*

Introduction

A recently published randomized controlled trial of cognitive treatment, placebo, oxybutynin, bladder training and pelvic floor training in children with functional urinary incontinence [1] concludes that the 3.7 girls/boys ratio in the prevalence of clinically diagnosed over-

active bladder and dysfunctional voiding, the co-existence of urinary and fecal incontinence, and the response to cognitive behavioural therapy (very similar to that of adolescents with stress-related conditions [2,3]) all point to social stress as an important etiological factor. This change in thinking about the etiology of functional incontinence in neurologically normal children has been introduced by a paper of Franco and co-workers [4] along with implications for assessment and management of functional incontinence.

Only recently, the time-honored link between social stress and changes in bladder activity [5,6] became unraveled by the finding that corticotropin-releasing factor (CRF), the activator of the hypothalamic-pituitary-adrenal axis, also acts as a neurotransmitter for CRF-receptors in the sacral parasympathetic neurons projecting to bladder and colon.

We wanted to re-appraise the role of social stress in functional incontinence in children by reviewing the most important research papers about the CRF signaling pathway and bladder/colon activity. Male and female animal models for the effects of social stress on both bladder and colon activity have been developed, and these could help us understand the pathophysiology behind functional incontinence in humans. They also might help to find a more adequate treatment than medication or elaborate training.

Stress and stressors

Everyone has personal recollections about certain emotions – *e. g.* prior to school tests [7]- inducing temporary detrusor overactivity. The opposite, temporary inhibition of voiding and/or defecation, is also a common human experience, induced by submission or subordination: quite a few novels describe how a middle-class suitor invited into the upper-class surroundings of his fiancée's parents spends the weekend constipated, asking for the bathroom as infrequently as possible [8]. Apparently, the type of stressor can dictate whether facilitation or inhibition will be provoked: anxiety and tension are associated with the former, dejection and defeat with the latter [9].

However, because the dominant-subordinate paradigm is a major stressor in males only, and far less in females, the response to a stressor will also differ between genders. Haller [10] subjected aggressive male and female rats to social defeat (resident-intruder) and also to social instability (isolation alternated with crowding): defeat was stressful mainly in males and social instability was the major stressor in females, judged by basal cortisol levels and objective signs of adrenal hypertrophy (Table 1).

	Resident-Intruder	**Novel Environment**
	Social Defeat	**Social Instability**
Male rat		
adrenal weight	Increased	no change
basal cortisol	increased	no change
Female rat		
adrenal weight	no change	increased
basal cortisol	no change	increased

Table 1: *Cross-tabulation of changes in adrenal weight and basal cortisol levels in aggressive rats following exposure to social stressors, for male and female animals [10].*

In controlled experiments with male and female mice [11], only the females responded to a mild social stress (a novel environment) with an increased fecal pellet rate, not the males (Table 2).

	Resident-Intruder	Novel Environment	Peripheral CRF-
	Social Defeat	**Social Instability**	**Injection**
Male rat/mouse			
detrusor activity	Underactivity [29-31]	not available [11]	Underactivity [33]
Fecal pellet rate		no change [11]	
Female rat/mouse			
detrusor activity	not available	Overactivity [11]	Overactivity [33]
fecal pellet rate		Increased [11]	

Table 2: *Cross-tabulation of changes in detrusor activity and fecal pellet rate in rodents, after exposure to social stressors [11,29-31] and after peripheral injection of corticotropin releasing factor [32,33], for male and female animals.*

Corticotropin releasing factor

Renewed interest in the classical response to stress - 'fight-or-flight' activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis - started with the isolation of corticotropin releasing factor [12], a hypothalamic peptide that stimulates release and synthesis of adrenocorticotropic hormone (ACTH) and β-endorphin from the anterior pituitary, which it reaches via the hypothalamic portal circulation. Phylogenetically, the genes encoding for the corticotropin releasing factor (CRF) peptides are highly conserved throughout evolution, back to invertebrates [13].

The ACTH-signal reaches the adrenals through the blood stream, triggering release and synthesis of cortisol; the plasma-level of cortisol has a distinct circadian rhythm, governed by a negative feedback via glucocorticoid receptors (GRs) in hippocampus, hypothalamus, and pituitary [14].

A recent meta-analysis of the effects of exposure to chronic stress (war/combat or abuse/assault) reports that such exposure results in a lower concentration of morning cortisol and a higher output across the rest of the day, which implies a flattening of the circadian output rhythm. The longer the interval between exposure and cortisol measurements, the more pronounced the blunting of the cortisol output - short intervals may show an output higher than normal [14]. The adjective 'chronic' in 'chronic stress' usually implies that the stressor persists over an extended period of time, but it also covers a short extremely stressful period that long afterwards still is perceived as threatening, whenever a new stressful event occurs; this perception depends on whether the original trauma is remembered particularly well - with the possibility of over-interpreting other stressors as trauma-related - or only in broad general terms, as a defensive coping strategy [15].

CRF signaling pathways

Much of this research was done in rodents, to find animal models for novel treatment of patients with unipolar depression [16], post-traumatic stress disorder [14,17-19], burn-out [13], substance abuse and addiction [13], and functional bowel and bladder disorders [13,20].

This research disentangled the neuronal CRF signaling pathways: CRF is a neurotransmitter, targeting two main receptors for corticotropin releasing factor, CRF1 and CRF2, which belong to the class of G protein-coupled receptors, implying relay of receptor activation to a host of different intracellular effectors.

Various CRF1 and CRF2 agonists and antagonists have been developed and tested, via intraperitoneal (ip), intrathecal (ith), and intracerebroventricular (icv) administration, to understand the physiological role of CRF signaling pathways [21,22]. CRF agonists and antagonists do not cross the blood-brain barrier easily [13,23]: the ip and ith routes will predominantly influence the peripheral parts of the CRF signaling pathway, far less the central parts that activate the sympathetic nervous system and the HPA-axis.

Central distribution of CRF and CRF-receptors

In adult rats, brain areas with CRF-immunoreactive (ir) neurons and neurons that express messenger RNA (mRNA) for CRF include the parvicellular area in the hypothalamic paraventricular nucleus (PVN), the cerebral cortex, the amygdalar-hippocampal complex, and Barrington's nucleus in the dorsolateral pons. CRF neurons in the central amygdala (part of the limbic system, for processing and saving emotional reactions) project to the PVN, the locus coeruleus (catecholaminergic neurons involved in arousal and attention shift) and the parabrachial nucleus in the pons (gustatory processing, part of the ascending reticular activating system). CRF-neurons in the bed nucleus of stria terminalis project to the dorsal vagal complex [13,20]. Globally, there is a correlation of the distribution of CRF-ir neurons in the brainstem between humans and rodents [22]. Barrington's nucleus in the dorsolateral pons (M region, pontine micturition center) is active prior to and during voiding, and a region in the ventral pontine tegmentum (L-region) is active in withholding voiding [24]. The neurons in Barrington's nucleus are synaptically linked to bladder and genitals, as well as to the distal colon [13,20].

The CRF1-receptor is distributed throughout the cerebral cortex, cerebellum, olfactory bulb, medial septum, hippocampus, amygdala and pituitary. As yet, central CRF2-receptors have been found only in the lateral septum and the hypothalamus [13,20].

Peripheral distribution of CRF and CRF-receptors

CRF is prominently expressed in the descending pathway from Barrington's nucleus down to the parasympathetic bladder and colon neurons in the intermediolateral cell columns in the sacral spinal cord, and to motoneurons in Onuf 's nucleus [25,26] in the anterior columns of the sacral spinal cord. Afferent loops in the CRF-signaling pathways are indicated by CRF expression both in bladder nerve fibers and urothelial cells [27], and in colonic epithelium and myenteric plexus [2,13]. CRF2-immunoreactive cells and cells that express CRF2 mRNA are widely distributed in peripheral tissues, including heart, lung, vasculature, skeletal muscle, upper gastrointestinal tract, and urogenital tract [13,16,27]. Expression of CRF1 has not been demonstrated in the urogenital tract, but CRF1 is prominently present in both the colonic myenteric plexus and the colonic epithelium [13,23].

In summary, there is compelling evidence that the CRF signaling pathway between Barrington's nucleus/locus coeruleus and the parasympathetic motoneurons in the sacral spinal cord facilitates or inhibits bladder and colon activity, over-riding the normal reflex activity of bladder and colon, as a net result of the processing of stressors in the central part of the CRF signaling system [13,20]. In the afferent loop of this signaling pathway, neurons in Barrington's nucleus respond to both bladder and colonic distention with CRF-expression [13,20].

Animal models for facilitation/inhibition of bladder and colonic function induced by social stress

The assessment of studies in experimental animals on stress-induced overactivity or under-activity of bladder and colon - possible models for functional incontinence in children - is hampered by a number of confounders: animal species and developmental stage, animal pretreatment, animal gender, injection of stressor *versus* CRF, as well as the circadian phase chosen for the actual experiment.

Animal species and developmental stage

Most publications on social stress in experimental animals have been done in rodents: adult rats or mice. Rats and mice live in communities, and are more likely to respond to social stressors than cats - cats are lone predators, not social animals. Species differences in CRF and CRF-receptor distribution between mice and rats are minimal, while the intermediolateral cell columns in the sacral spinal cord differs considerably between cats and rodents [26,27]. To minimize influences from developmental stages [28], most researchers favor adult animals.

Stressor and male gender

The dominant-subordinate paradigm is commonly applied as a standard social stressor in male experimental animals. Originally used by Desjardins and co-workers as a social ranking experiment in normal male mice [29], with voiding frequency and voided volume as outcome variables (blotting of all individual voidings), it is now generally used in a resident-intruder set-up. The defeated or subordinate male animal always responds to the stressor with a markedly decreased number of voidings and a corresponding increase in voided volume [29,30], accompanied by an increase in bladder mass [30].

Chang and co-workers redid Desjardins's social ranking experiment in male mice, in a normal resident *versus* aggressive intruder set-up, with blotting of voidings as well as cystometric data as outcome variables; in the defeated mice, cystometric bladder capacity and voided volume increased but voiding pressures remained normal. They also documented structural changes in the bladders of the defeated mice, resembling those that appear with infravesical obstruction [31].

Kiddoo and co-workers injected ovine CRF, more potent with CRF1 than with CRF2 receptors, and a selective CRF2 receptor agonist (urocortin 2), ip and ith, in normal male rats. Their cystometric outcome showed a decreased voiding frequency, with increased micturition volume and bladder capacity, after ith injection of ovine CRF or urocortin 2 [32].

Haller's experiments [10] with male and female aggressive rats, both in a resident-intruder set up (social defeat) and subjected to alternated isolation and crowding (social instability), made it clear that the dominant-subordinate paradigm is a gender-specific stressor: only male rats responded to social defeat with increased basal cortisoland adrenal cortical hypertrophy, while female rats showed this response only to social instability (Table 1).

Stressor and female gender

Apparently, social instability is also a gender specific stressor, which is corroborated by the experiments of Million and co-workers [11]: they subjected male and female CRF-overexpressing mice (chronic stress) to mild social instability, a novel environment, with fecal pellet rate and blotting of voidings as outcome variables. Only the female mice responded with an increased fecal pellet rate, an increase in number of voidings, and a decrease of voided volumes; the male mice responded with the same pellet rate as their controls, but in this particular set up data on voided volume and voiding frequency were not collected.

Klausner and co-workers subjected normal female rats to injections with CRF and a CRF-antagonist (astressin), ith, ip, and icv, with blotting of voidings as well as cystometric data as outcome variables. They found a dose-related decrease in voided volume and increase in number of voidings with ith and ip CRF injections, which could be blocked by astressin; cystometrically, bladder capacity and micturition treshold were decreased after CRF injection, ith and ip (Table 2) [33].

Circadian phase of experiment

As mice and rats are night-animals, running around and foraging for food during our human night, it makes sense to expose them to social stress during their activity phase: in that phase, state of arousal, blood pressure, body temperature, metabolism, urine production and gastro-intestinal acitivity are all on a higher level than in the inactivity phase. Kiddoo and co-workers [32] pointed out the importance of the state of arousal in interpreting cystometric parameters in rats, and the recent paper of Negoro and co-workers made it clear that bladder muscle cells have an internal clock, governing functional bladder capacity during activity and inactivity [34].

Only Desjardins and co-workers [29] performed their experiments in the rodent's activity phase, the dark part of a 14h:10h light: dark cycle (lights out at 19:00, lights on at 05:00) - every other study quoted in this paper was done in the human light part of a 12:12 light: dark cycle, the rodent's inactivity phase. In defining an experimental rat or mouse model to understand the effects of social stress on human bladder/colon, the first thing to investigate is whether the outcome of such experiments is independent of the circadian phase the experiments take place in [35,36].

Gender-specific models for overactive bladder and hinman's syndrome

The outcomes of the experiments described above can best be compared by cross-tabulating the changes in detrusor activity, for male and female animals separately, for social defeat, social instability, and peripheral CRF-injection (Table 2). From the detrusor responses in table 2, we have to conclude that the response to peripheral CRF is gender specific – Haller's findings [10] in aggressive male and female rats exposed to social defeat and social instability confirm the gender specificity of the stressors.

Looking for parallels of these responses in humans, we have to account for this gender specificity: the inhibition of detrusor activity with concomitant structural changes in the bladder wall in male rodents could be a model, as pointed out by Chang [31] and Wood [30], for Hinman's syndrome [37], which occurs almost exclusively in boys. Inhibition of detrusor activity in male rodents is less well suited as a model for 'voiding postponement' [20], because that condition is described as voluntary inhibition, in girls as well as boys, without concomitant structural changes in the bladder wall [38]. Detrusor overactivity as a response to social stress in female rodents could very well serve as a model for overactive bladder in girls: in children, urgency with urinary incontinence occurs with a female-to-male ratio of 4 to 1 [1,39]. It could also serve as a model for urge incontinence in adult female patients.

Simultaneous changes in bladder and colonic function

Million and co-workers [11] exposed CRF-overexpressing male and female mice (chronic stress) to a novel environment. They noted that the females responded with both bladder and colon overactivity, judged by number of voidings and voided volume (blotting), and by a fast and short increase in fecal pellet rate; the female mice also responded with a marked increase in ambulatory activity. In the male CRF-overexpressing mice, ambulatory activity did not increase after exposure to the social stressor, and the increase in fecal pellet rate was not statistically significant compared to controls – because the female mice were far more responsive to the novel environment than the male, changes in the blotting pattern of voidings were not evaluated in the male mice.

Larauche and co-workers [23] injected a moderately selective CRF1 agonist (cortagin) ip in normal male rats and mice, with fecal pellet rate and colonic manometry as outcome variables. In both male rats and mice, cortagin ip increased the fecal pellet rate, provoked diarrhea, and decreased the manometrically measured colonic transit time concomitant with an increase of colonic motility. The difference in outcome between Million's [11] and Larauche's observations could be gradual, owing to the weakness of Million's social stressor in male and female mice relative to Larauche's cortagin injection in male mice, given at the maximal effective dose to obtain visceral hypersensitivity.

That said, the point of interest is that in rodents social stress can induce facilitation of bladder and colon activity via the CRF-signaling pathway simultaneously - as yet without obvious gender specificity – and that children with functional urinary incontinence have a significant comorbidity (32%) from functional fecal incontinence [40].

Prerequisites for modeling effects of social stress on bladder and colon emptying

The first prerequisite for a rodent model is to find out the influence of the circadian phase chosen for the actual experiment: as rodents are night-animals, the best set-up is the one chosen by Desjardins and co-workers [29], the dark part of the human 14h:10h light: dark cycle.

Resident-intruder (social defeat) and switches between environments (social instability) are commonly used as stressors in rodents, but it might be possible to devise other social stressors that mimic human situations. For example, teaching rats how to handle a maze with food as reward could be an equivalent of human anxiety for an important school-test.

The gender-specificity of the responses to stressors as well as to peripheral CRF injections implies that all experiments have to be carried out with both male and female rodents, in one and the same set up.

To collect data on voiding (volume and frequency) and defecation (volume and frequency) it might not be necessary to carry out cystometry and colonic manometry. Blotting of each individual voiding and counting fecal pellets are safe and simple alternatives, judged by the experiments discussed in this paper. A great improvement on simple blotting is the 'automated voided stain-on-paper method,' described by Negoro and co-workers. This method can accurately record the µl-volumes voided by a mouse, over several days, allowing records of the murine circadian diuresis rhythm [34]. Automated detection of fecal pellet rate could be added to this set up.

Conclusions

More insight in pathophysiology and etiology of urinary and fecal incontinence in children is to be gained from social stress-induced changes in bladder and colon activity in rodent models. Genetically, these models are homologous for the human CRF signaling pathway [13], and new models could be developed on the published templates. Existing models for overactive bladder already comply with two important characteristics of children with functional incontinence: gender specificity and co-existence of urinary and fecal incontinence.

The synchrony in the rodent models between application of the stressor and the occurrence of overactivity of bladder and colon may also be present in children with functional incontinence. We could start by learning more about this synchrony between the occurrence of episodes with overactive bladder (or inhibited voiding) and exposure to social stressors.

Instead of using self-reported questionnaires, we should screen for behavioral and/or emotional risk connected with social stress with teacher rating scales, recently developed for school age children [41].

Self-reported incontinence lacks objectivity, and we need to document urinary incontinence over extended periods of time: feasible, in this day and age of wearable and epidermal electronics [42,43], by using children's underwear with a woven-in sensor for humidity (or temperature), connected to a data-logger or iPhoneTM app that records the sensor's output over time.

In adolescents and adults, exposure to traumatic episodes during childhood may result in lasting changes in the HPA-axis reactivity, which could explain why any new stressful event occurring later in life may 'replay' the childhood-experience [15,44-47]. It is tempting to apply this hypothesis to social stressors in children, but school-age children do not have a long enough interval between the first trau-

matic episode and new episodes of social stress. Nevertheless, childhood and adolescent abuse significantly increased the odds of urgency and frequency in the Boston Area Community Health survey, a community-based epidemiological study on urologic symptoms and risk factors in adults aged 30-79 years [48].

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