Neuroscience and Biobehavioral Reviews 51 (2015) 1–14

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Developmental programing of thirst and sodium appetite

Andre S. Mecawi[a,b], Ana F. Macchione[c,d], Paula Nuñez[e], Carmen Perillan[e], Luis C. Reis[a], Laura Vivas[c,f], Juan Arguelles[e,*]

[a] Department of Physiological Sciences, Institute of Biology, Federal Rural University of Rio de Janeiro, Seropedica, Brazil
[b] Department of Physiology, Faculty of Medicine, University of Malaysia, Kuala Lumpur, Malaysia
[c] Institute of Medical Investigation Mercedes and Martín Ferreyra, INIMEC-CONICET-National University of Cordoba, Cordoba, Argentina
[d] Department of Cellular Biology, Faculty of Dentistry, National University of Cordoba, Córdoba, Argentina
[e] Department of Functional Biology, Neuroscience Institute of Asturias (INEUROPA), Faculty of Medicine and Health Sciences, University of Oviedo, Oviedo, Spain
[f] Department of Physiology, Faculty of Exact, Physical and Natural Sciences, National University of Cordoba, Córdoba, Argentina

ARTICLE INFO

Article history:
Received 10 July 2014
Received in revised form 5 December 2014
Accepted 9 December 2014
Available online 17 December 2014

Keywords:
Thirst
Sodium appetite
Developmental programing
Renin–angiotensin system
Lifestyle
Epigenetic
Neuroendocrine

ABSTRACT

Thirst and sodium appetite are the sensations responsible for the motivated behaviors of water and salt intake, respectively, and both are essential responses for the maintenance of hydromineral homeostasis in animals. These sensations and their related behaviors develop very early in the postnatal period in animals. Many studies have demonstrated several pre- and postnatal stimuli that are responsible for the developmental programing of thirst and sodium appetite and, consequently, the pattern of water and salt intake in adulthood in need-free or need-induced conditions. The literature systematically reports the involvement of dietary changes, hydromineral and cardiovascular challenges, renin–angiotensin system and steroid hormone disturbances, and lifestyle in these developmental factors. Therefore, this review will address how pre- and postnatal challenges can program lifelong thirst and sodium appetite in animals and humans, as well as which neuroendocrine substrates are involved. In addition, the possible epigenetic molecular mechanisms responsible for the developmental programing of drinking behavior, the clinical implications of hydromineral disturbances during pre- and postnatal periods, and the developmental origins of adult hydromineral behavior will be discussed.

Contents

Abbreviations: ACE, angiotensin converting enzyme; ALD, aldosterone; ANG II, angiotensin II; ANP, atrial natriuretic peptide; AP, area postrema; AT_1, angiotensin receptor type 1; AT_2, angiotensin receptor type 2; AVP, vasopressin; CVO, circumventricular organ; DRN, dorsal raphe nucleus; HSD2, 11 beta-hydroxysteroid dehydrogenase type 2 enzyme; ICV, intracerebroventricular; LPBN, lateral parabrachial nucleus; LT, *lamina terminalis*; MnPO, median preoptic nucleus; NTS, nucleus of the solitary tract; OVLT, *organum vasculosum* of the *lamina terminalis*; PEG, polyethylene glycol; PVN, paraventricular nucleus; RAAS, renin–angiotensin-aldosterone system; SFO, subfornical organ; SHR, spontaneously hypertensive rats; SON, supraoptic nucleus.

* Corresponding author. Tel.: +34 985106245; fax: +34 985106285.
E-mail address: jal@uniovi.es (J. Arguelles).

http://dx.doi.org/10.1016/j.neubiorev.2014.12.012
0149-7634/

1. Introduction

The loss or gain of body water and sodium, which occurs during different states of fluid disturbance, elicits reflexive and behavioral responses that equilibrate the rate of fluid depletion or expansion, ultimately restoring body fluid levels. To activate the appropriate homeostatic responses, the central nervous system must receive and integrate multiple types of sensory input from specialized receptors that monitor the body fluid status. These signals are detected by taste receptors, peripheral osmo/Na^+-receptors, volume receptors and arterial/cardiopulmonary baroreceptors, which activate the nucleus of the solitary tract (NTS; Vivas et al., 2013), the *lamina terminalis* (LT), and one of the sensory circumventricular organs (CVOs), the area postrema (AP). The LT comprises the median preoptic nucleus (MnPO) and two other sensory CVOs: the subfornical organ (SFO) and the *organum vasculosum* of the *lamina terminalis* (OVLT; Antunes-Rodrigues et al., 2004). The SFO and OVLT are devoid of the blood–brain barrier, and both contain cells that are sensitive to humoral signals, plasma and cerebrospinal fluid (CSF) sodium concentrations (Vivas et al., 1990; Noda, 2006), osmolality (Sladek and Johnson, 1983) and angiotensin II (ANG II) levels (Simpson et al., 1978). The LT, AP and NTS modulate neural circuitry, which includes integrative areas such as the paraventricular (PVN), supraoptic (SON), lateral parabrachial (LPBN) and dorsal raphe (DRN) nuclei. In this context, the modulation of water and sodium intake involves interactions between the CVO receptive areas (LT, AP, and NTS), the serotonergic pathways from the DRN, the gustatory information from the LPBN and the OTergic/AVPergic pathways within the SON and PVN (Fig. 1). Once these signals act on the above-mentioned neurochemical networks, they trigger the appropriate sympathetic, endocrine and behavioral responses to restore the hydromineral balance (Vivas et al., 2013).

In pregnancy, several adaptations in maternal hemodynamic, hormonal and biochemical variables occur that allow for normal fetal growth and development. Studies conducted in recent decades have produced evidence to support the importance of the environment during sensitive periods of gestation and early postnatal life. The consequences of the developmental environment might persist until adulthood, affecting tissue structure and function. In fact, research has shown that this process, known as "developmental programming," might result in adult diseases; this hypothesis is often called "developmental origins of adult disease" (Barker et al., 2002). Barker and colleagues formulated this hypothesis based on observations collected from economically poor regions of England with (i) the highest rates of infant mortality due to malnutrition, mainly in the early 20th century, and (ii) the highest rates of mortality from coronary heart disease some decades later (Barker and Osmond, 1986). More recently, a large amount of research has been carried out to evaluate how the adult phenotype is a consequence of environmental signals operating on genes during development.

It is possible that the so-called "programming phenomenon" is a type of "phenotypic plasticity" for the expression of different phenotypes from the same genotype. Thus, this phenomenon is due to pre-existing genetic variations and is the result of the interaction of a variety of environmental events such as adaptation, developmental programing and epigenetic alterations. The ultimate goal of this type of process is to provide a strategy to adapt to a constantly fluctuating environment, minimizing the genotypic disadvantage that each individual might have in relation to its surroundings (Brakefield et al., 2005).

The hydroelectrolyte homeostatic systems that regulate thirst and sodium appetite are not exempt from developmental programing effects. Many studies indicate that during sensitive periods of ontogeny, different pre- and/or postnatal challenges modify fluid intake patterns of offspring during development and in adulthood in need-free and/or need-induced conditions (Arguelles et al., 2000; Perillan et al., 2007; Mecawi et al., 2009; Leshem, 2009a,b; Macchione et al., 2012).

In view of these findings, the literature regarding the ontogeny of the mechanisms related to ingestive behavior, i.e., thirst and sodium appetite, and how developmental challenges can alter the lifelong patterns of water and salt intake will be reviewed. The potential neuroendocrine and molecular mechanisms responsible for the programing of drinking behavior, as well as the possible clinical implications, will also be addressed.

2. Ontogeny of thirst and sodium appetite

Early development is considered a crucial period for the establishment of behavior. In the rat, the mechanisms responsible for drinking make their first appearance abruptly and sequentially at critical ages. Wirth and Epstein (1976) showed that newborn rats could not be made to drink water in response to any known stimulus of thirst but that drinking could be induced by cellular dehydration at postnatal day 2, by hypovolemia at postnatal day 4, and by isoproterenol at postnatal day 6. ANG II-induced intake undergoes a similar ontogenetic progression. Drinking in response to intracranial ANG II occurs at postnatal day 2, but at this stage, the pups cannot distinguish between milk and water (Ellis et al., 1984). However, by postnatal day 8, the adult response has appeared, and the pups drink more water than milk in response to intracranial ANG II administration (Ellis et al., 1984). Thirst elicited by activation of the brain renin–angiotensin system (RAAS) in the suckling rat becomes more specific to water after 16 days (Leshem et al., 1988), and the mechanisms of thirst aroused by renin or intracellular dehydration are fully developed before weaning (Leshem and Epstein, 1988).

Accordingly, rat pups develop the thirst mechanism during a period when they are still completely dependent on their mother's milk and before they need these mechanisms because maternal milk ensures the pup's hydration and nutrition. When rat pups exhibit thirst during their life, they lap and swallow, repeatedly opening their mouths in a different motor pattern from that of suckling. Thus, it is clear that the neural mechanisms for thirst and the act of drinking are innate (Fitzsimons, 1998).

At present, there are no experimental data investigating the postnatal ontogeny of thirst in humans, so it is currently unknown to what extent thirst is "hard-wired" at birth. One unexplored possibility is that there is little differentiation between hunger and thirst in newborn animals, at least in mammals, given that in this case, the developmental system of food/fluid intake involves both needs being met simultaneously via the ingestion of breast milk. If this is the case, then because the food/fluid intake seems to be developed in newborns (Ellis et al., 1984), mammals might have to learn to differentiate hunger and thirst later in development, either during or post weaning, when both supplies are differentiated (Hall et al., 2000).