Activity-Dependent Neuroprotective Protein

Subjects: Biochemistry & Molecular Biology | Neurosciences
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The activity-dependent neuroprotective protein (ADNP), a double-edged sword, sex-dependently regulates multiple genes and was previously associated with the control of early muscle development and aging.

Keywords: ADNP ; NAP ; muscle function ; CatWalk ; gene expression

1. Introduction

As detailed in our recent publication (https://www.mdpi.com/1422-0067/21/18/6715/htm#B53-ijms-21-06715): The activity-dependent neuroprotective protein (ADNP)[1][2], partly controlled by vasoactive intestinal peptide (VIP) and pituitary-adenylate cyclase activating polypeptide (PACAP)[3][4][5][6][7][8][9], is a known major regulator of gene function[10]. For example, our original studies showed that Adnp regulates more than 400 genes during embryonic development including genes controlling the development of the visceral endoderm, the heart and organogenesis in general[11]. In the adult mouse, Adnp regulates hundreds of genes important for brain and immune functions [12][13]. Importantly, there is a significant resemblance between mouse and human ADNP gene regulation [13][14][15]. The resemblance is further accentuated by the fact that mouse Adnp mRNA is 90% identical to human ADNP mRNA[2]. Indeed, the Adnp-deficient heterozygous (haploinsufficient) mouse model[16] predicted the autism-intellectual disability—associated ADNP syndrome[13].

Delayed motor development characterizes a large majority (96%) of ADNP syndrome children, suffering from de novo mutations in ADNP[14][17][18]. ADNP syndrome motor deficiencies manifest as hypotonia as well as opposing acute muscle tightness, signs of atrophy and abnormal gait[17][18]. The human pathological condition was mimicked by the mouse model of Adnp haploinsufficiency[13], exhibiting reduced muscle tone, as was demonstrated in the hanging wire and grip strength tests, along with gait deficits as established by the CatWalk gait analyses[13].

We have also shown that the expression levels of ADNP and its paralogue protein ADNP2 in the vastus lateralis and bicep brachii muscles are significantly upregulated in the human elderly population, compared to young subjects, in a sex dependent manner. Thus, in the vastus lateralis ADNP is increased with aging in males and females, while ADNP2 is increased with aging in females only. In the bicep brachii muscles, ADNP is increased with aging only in males and not in females, while ADNP2 is increased with aging exclusively in females[19]. ADNP expression was highly correlated with 24 genes, with nicotinamide nucleotide adenylyl (NAD) transferase 1 (NMNAT1) being the leading gene/protein[19]. As such, NMNAT1-associated regulation of NAD^+ salvage capacity in human skeletal muscle declines with aging, suggesting a causative or a compensatory role for ADNP content [20].

Importantly, not only the skeletal limb muscles are affected in the ADNP syndrome. For example, the bladder is slow in development with 81% of children suffering from the syndrome, exhibiting bladder training delay, and many are still not toilet trained when approaching puberty[17]. Another key characteristic of ADNP syndrome is speech delay, which presented in 98.6% of individuals and 19% had no language development at all[17]. Apraxia and absence of tongue movement was also found[18].

Mechanistically, ADNP is found in the nucleus as well as in the cytoplasm, and cytoplasmic representation increases in mature neurons, where ADNP is essential for neurite maintenance[21]. As such, ADNP exerts its control by regulating microtubule dynamics, binding to microtubule end binding proteins EB1 and EB3[22], also regulating Tau-microtubule interaction[23][24]and axonal transport[12]. Importantly, cytoskeletal reorganization is associated with stretch-induced gene expression, implicating a role for cytoplasmic ADNP in gene expression regulation as well[25], especially in stretch-associated muscle cells.

Adnp deficiency is also associated with reduced autophagy that is dependent on microtubule integrity[26], with ADNP binding the microtubule associated protein 1 light chain 3B (LC3B), forming the autophagosome[27]. Interestingly, several muscle diseases present microtubule/autophagy deficits. For example, Duchenne muscular dystrophy (DMD)[28][29][30][31],

Becker muscular dystrophy (BMD)[30][32][33], exhibiting absence or mutations in dystrophin, and tibial muscular dystrophy (TMD), exhibiting mutations in titin[34]. Furthermore, the ADNP regulating neuropeptide PACAP[3] was also shown to protect muscle function in a model of spinobulbar muscular atrophy (SBMA)[35].

The cytoplasmic interactions of ADNP with LC3 and EB1/EB3 are enhanced in the presence of the ADNP snippet, NAP (NAPVSIPQ, also known as CP201) containing an EB1/EB3 and self-interacting SxIP motif [12][23][24][26][27]. Moreover, through EB1/EB3 interactions, NAP enhances Tau-microtubule binding, protecting against tauopathy [23][24], which has also been found in the SOD1-G93A mouse model of the neuromuscular disorder, amyotrophic lateral sclerosis (ALS)[36].

Given the significant effect of ADNP mutations and ADNP deficiency on motor functions[13], and the strong association of ADNP with gene regulation (e.g., [10][11][21]), we hypothesized that it is involved in direct regulation of versatile muscle genes, with expression levels correlating with motor function throughout development. Our results have proven our hypothesis and identified multiple biomarkers for Adnp muscle activity.

2. Adnp expression and multi-muscle gene expression

In the current paper we have discovered extensive correlation between Adnp expression and multi-muscle gene expression throughout life, with sex-specific patterns. Adnp-deficient gene regulation was corrected by its active site protein fragment, drug candidate NAP. Mechanistically, Adnp gene regulation was correlated with CatWalk motor behavioral outcomes.

Further referring to the mechanism, our original studies identified a high degree of correlation between ADNP and NMNAT1 in the human muscle[19]. Here, a high correlation was discovered between Adnp and Nmnat1 expression in the young male mouse muscle. NMNAT1 regulates NAD+ salvage capacity in human skeletal muscle, which is declining with aging[20].

Additionally, here, in the GC muscle, Adnp correlated with Adnp2 only in the older mouse groups in a sex-dependent manner (appearing earlier and showing stronger correlations in the females). Previous findings linked dysregulation of Adnp/Adnp2 correlations with aberrant synaptic function in neuropsychiatric diseases[37]. Interestingly, sexual differences were found in ADNP, ADNP2 expression in Alzheimer's disease (lymphocytes) [38] and in schizophrenia (postmortem brains and lymphocytes)[27][37]. While ADNP2 is a less studied gene compared to ADNP[2][39][40], recent studies have also linked ADNP2 deletion (together with other genes) to autism[41]. Further studies tied ADNP2 to osteoblast regulation[42], suggesting pleiotropic activities, similar, and potentially complementary to ADNP.

Adcyap1r1 encoding the PACAP-specific, PAC1 receptor, did not correlate with Adnp in the bladder, despite the significant increase seen in the Adnp+/− females compared to Adnp+/+ females and the amelioration with NAP treatment. These findings are of significant interest, as intra-bladder administration of the PAC1 receptor antagonist, PACAP(6–38), reduces urinary bladder frequency and pelvic sensitivity in mice exposed to repeated variate stress[43], with PACAP ameliorating Adnp-deficiency exacerbated stress response[3]. While ADNP was directly linked to cognitive impairment/language acquisition in humans[14][17][44] and in mice (vocalization)[13], indirect evidence also ties PACAP to the vocalization response[45]. We also participated in a study showing that PACAP regulates muscle function in protection against outcome measures in a mouse model of spinobulbar muscular atrophy (SBMA)[35].

Interestingly, here, we also found sexually/developmentally differential expression of Myl2 and Myl9 in correlation with Adnp expression. In this respect, MYL2 is linked to cardiac development and function[46], while MYL9 is involved in smooth muscle and non-muscle cell contractile activity e.g., in the gut and urinary tract[47], with ADNP syndrome children suffering cardiac as well as gastrointestinal problems[17]. Furthermore, a recent study identified Myl9 as highly important for skeletal muscle development[48] as well as to bladder and gastrointestinal smooth muscle contraction, with homozygous deletion leading to megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), a severe disease characterized by functional obstruction in the urinary and gastrointestinal tract[47][49]. Anatomically, the bladder divides into two parts: the dome and the base. The dome of the bladder is made up of smooth muscle, and the base consists of a trigone and neck that are closely connected to the pelvic floor. There are two urethral sphincters at the bladder outlet that are necessary for normal voluntary micturition [50]. Myl9 may be associated with the sphincters as well as the smooth muscle function. Together with the current findings, MYL9 may play a significant role in skeletal as well as smooth muscle regulation in the ADNP syndrome.

Similarly, Foxp2 is implicated as critical for central control for normal bladder voiding behavior[51] and may be important to tongue movement function[52], both affected in the ADNP syndrome. Indeed, Foxp2 showed distinct sexual dichotomy in the tongue. Further sexual differences were observed in Foxp2 also in correlation with Catwalk performance. Previous studies have indicated a close correlation of the Foxp1/Foxp2 transcript expression and regulation of ultrasonic

vocalization in mice. Foxp1 and the androgen receptor are co-expressed in striatal medium spiny neurons and brain-specific androgen receptor KO (ArNesCre) mice exhibit reduced Foxp1 expression in the striatum at E17.5 and P7.5 and an increased Foxp2 level in the cortex at P7.5[53]. Our previous bioinformatics results showed ADNP regulation of steroid pathways[15] and our current results suggest that this may be extended to the specific muscle cells. Furthermore, this steroid regulation may be linked with the higher prevalence of autism in boys compared to girls[54], with ADNP being a major autism driving gene[54][55]. Future research should further aim to decipher ADNP precise involvement in muscle function including cardiac and gastrointestinal muscles and use age and sex-dependency as major impacting study design and research outcome covariates.

While NAP treatment corrected many of the Adnp+/− associated deficiencies, it did not correct all, as we have previously observed, also in other organs[13]. This could be due to additional differential temporal and sex-dependent controls exerted on these genes by Adnp and other regulatory proteins. One example is Akap6 suggested as an important regulator of myoblast differentiation, myotube formation, and muscle regeneration [56]. Thus, further studies are required to elucidate the potential interactions between Akap6 and Adnp.

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