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JOURNAL OF PROTEOMICS XX (2012) XXX-XXX



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# Proteomic characterization in the hippocampus of prenatally stressed rats

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#### 12 A R T I C L E I N F O

13 Article history:

- 18 Received 22 August 2011
- 19 Accepted 12 December 2011
- 26 \_\_\_\_\_
- 29 Keywords:
   30 Proteomics
- 33 Hippocampus
- 32 Early life stress
- 33 Programming
- 36 Animal model
- 27
- 36

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#### ABSTRACT

Rats exposed to early life stress are considered as a valuable model for the study of epigenetic programming leading to mood disorders and anxiety in the adult life. Rats submitted to prenatal restraint stress (PRS) are characterized by an anxious/depressive phenotype associated with neuroadaptive changes in the hippocampus. We used the model of PRS to identify proteins that are specifically affected by early life stress. We therefore performed a proteomic analysis in the hippocampus of adult male PRS rats. We found that PRS induced changes in the expression profile of a number of proteins, involved in the regulation of signal transduction, synaptic vesicles, protein synthesis, cytoskeleton dynamics, and energetic metabolism. Immunoblot analysis showed significant changes in the expression of proteins, such as LASP-1, fascin, and prohibitin, which may lie at the core of the developmental programming triggered by early life stress. © 2011 Elsevier B.V. All rights reserved.

39 1. Introduction

The low discordance of depression between monozygotic 40 41 twins and the slow progress in identifying genetic risk factors 42 suggest that epigenetic changes largely contribute to the individuals' vulnerability to major depressive disorder [1]. Both 43 human and animal studies suggest that exposure to stressful 44 events during critical periods of brain development triggers an 45 epigenetic programming leading to low resilience to stress in 46 the adult life [2–8]. Abnormalities of synaptic transmission 47 and plasticity in the hippocampus represent an integral part 48 of this epigenetic program. For example, early life stress 4950resulting from low maternal care in rodents causes a permanent reduction in the length of dendritic branching and the 51number of dendritic spines associated with an impairment 52

of synaptogenesis and long-term potentiation in the hippo- 53 campus [9–11]. This fits nicely with the clinical evidence that 54 poor parental care can compromise cognitive development 55 [12,13]. 56

Rats exposed to prenatal restraint stress (PRS) develop 57 long-lasting biochemical and behavioral changes that likely 58 reflect the induction of a pathological epigenetic program- 59 ming [14,15], and therefore represent a model that meets the 60 criterium of construct validity because it replicates environ- 61 mental factors implicated in the etiology of depression and 62 other stress-related disorders [1]. Alterations induced by PRS 63 comprise a dysfunction of the hypothalamo-pituitary-adrenal 64 (HPA) axis which is reversed by cross fostering at birth [16], a 65 generalized disorganization of circadian rhythms and the 66 sleep–wake cycle, an age-dependent impairment in spatial 67

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learning, a lifelong reduction of hippocampal neurogenesis, and 68 changes in the levels of brain-derived neurotrophic factor 69 (BDNF), cyclic-AMP responsive element binding protein (CREB), 70 and group-I and group-II metabotropic glutamate receptors in 71 the hippocampus [16-20]. Remarkably, some of these changes 72 are reversed by chronic antidepressant treatment [21-23]. 73 74 Hence, the rat model of PRS is particularly valuable for a systematic analysis of hippocampal proteins that are the product of the 7576 epigenetic programming leading to a low resilience to stress 77 and to an anxious/depressive phenotype in the adult life. Here, we examined the protein expression profile in the hippo-78 campus of adult rats exposed to PRS by using a proteomic ap-79 proach based on the use of two-dimensional electrophoresis 80 coupled with mass spectrometry. 81

#### 83 2. Materials and methods

#### 84 2.1. Animals

Nulliparous female Sprague–Dawley rats, weighing approximately 250 g, were purchased from a commercial breeder (Harlan). Animals were housed at constant temperature ( $22\pm2$  °C) and under a regular 12 h light/dark cycle (lights on at 8.00 a.m.). Pregnant females were randomly assigned to stressed or control groups (n=12 per group).

#### 91 2.2. Stress protocol

Animals were subjected to PRS according to our standard pro-9293 tocol [16,21]. From day 11 of pregnancy until delivery, pregnant female rats were subjected to three stress sessions daily (45 min 94 95 each), during which they were placed in transparent plastic cylinders and exposed to bright light. Only male offspring from lit-96 ters containing 10-14 pups with a comparable number of males 97 and females were used for the experiments. All experiments 98 followed the rules of the European Communities Council Direc-99 tive 86/609/EEC. The prenatal stress procedure was approved by 100 101 the local ethical committee.

# 102 2.3. Protein sample preparation and 2D analysis in the 103 hippocampus

Hippocampi of PRS and control rats (n=6/group) were rapidly 104105dissected, frozen on dry ice and stored at -80 °C. Samples were then homogenized with a glass/Teflon homogenizer at 106 a concentration of 10% (w/v) in a solubilizing solution contain-107 ing: 7 M urea (Sigma-Aldrich, St. Louis, MO, USA), 2 M thiourea 108 (Fluka, Buchs, Switzerland), 40 mM Tris (Sigma-Aldrich), 2% 109CHAPS (Fluka), and Complete™ protease inhibitor (Roche, 110 Basel, Switzerland). Samples were sonicated three times for 11110 s on ice with an ultrasonic processor with probe (Ultrasonic 112 2000, Dynatech Laboratories Inc., Chantilly, VA, USA). The ex-113 tract was centrifuged at 1000 g and the pellet discarded. An al-114 115 iquot of this supernatant was used to measure protein concentration by the Bradford method [24]. 100 µg of proteins 116 was separated by 2D electrophoresis following a step of pas-117sive rehydration on 18 cm immobilized pH gradient strips 118 (IPG; non-linear pH gradient of 3-10, GE Healthcare, France) 119 overnight. Focusing was carried out for 24 h at 20 °C for a 120

total of 100,000 Vh on a pHaser isoelectric focusing system 121 (Genomic solutions, Cambridgeshire, UK). The focused IPG 122 strips were equilibrated for 20 min with gentle shaking in an 123 equilibration solution (6 M urea, 2% SDS, 375 mM Tris pH 8.8, 124 30% glycerol) containing 1% DTT, and then with 2% iodoaceta-125 mide. The strips were applied to 10% SDS polyacrylamide gels 126 using the Investigator System (Genomic Solutions), and finally, 127 2D gels were silver-stained. For each animal, 2-D gel electropho-128 resis was performed in triplicates for a total of 36 gels. 129

Electrophoresis images of gels were digitized using the GS- 130 710 densitometer system (Bio-Rad). 2D gel analysis was car- 131 ried out with Progenesis SameSpots software (Nonlinear Dy- 132 namics, Ltd). 133

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2.4. Statistics

The aligned images were grouped into their corresponding 135 PRS or control group and the statistically ranked list of spots 136 was evaluated in the review stage of the SameSpots software. 137 Protein levels were evaluated as volumes (spot area×optical 138 density) for the protein spots matched among gels. Spot vol- 139 ume for valid spots was normalized to total density for each 140 gel. Our criteria for evaluation of protein spots were based 141 on an ANOVA p-value <0.05 as calculated with the built-in statistical tools in the software and a minimum of 1.5-fold inten- 143 sity (normalized volume) in protein content between PRS and 144 control animals. Then, only spots within the range of 1.5–3.5 145 fold change were cut out (24 spots) and processed for LC–MS/ 146 MS analysis. 147

#### 2.5. Protein identification with LC–MS/MS

The gel with the highest spot intensity was selected for man- 149 ual excision for evaluation by mass spectrometry. Spots of in- 150 terest were carefully cut from the gel, destained in a solution 151 containing 1.6% thiosulfate and 1% potassium ferricyanide, 152 extensively washed in water, and then submitted to in-gel 153 trypsin digestion. Briefly, after reduction and alkylation, tryp- 154 sin digestion was performed overnight at 37 °C in 25 mM am- 155 monium bicarbonate (porcine mass spectrometry grade MSG- 156 Trypsin; G-Biosciences, Agro-Bio, La Ferté St Aubin, France). 157 Peptides were extracted in 45% acetonitrile/45% water/10% tri- 158 fluoroacetic acid (TFA) (v/v/v) and then dried in a speed-vac 159 (Eppendorf) before nano-high pressure liquid chromatography 160 (HPLC)-MS/MS analysis. NanoLC-NanoESI-MS/MS analyses 161 were performed either on an ion trap mass spectrometer (LCQ 162 Deca XP+, Thermoelectron, San Jose, CA) equipped with a 163 nano-electrospray ion source coupled to a nano-flow high- 164 pressure liquid chromatography system (LC Packings Dionex, 165 Amsterdam, The Netherlands) as previously described [25], or 166 on an hybrid quadrupole time-of-flight mass spectrometer (Q-167 Star, Applied Biosystems, Foster City, California, USA) equipped 168 with a nano-electrospray ion source coupled with a nano HPLC 169 system (LC Packings Dionex, Amsterdam, The Netherlands). 170 Peptidic samples were dissolved in 5  $\mu L$  95% H2O/5% ACN / 171 0.1% HCOOH (v/v/v) (solvent A) and were injected into the 172 mass spectrometer using the Famos auto-sampler (LC Packings 173 Dionex, Amsterdam, The Netherlands). Samples were desalted 174 and concentrated on a reserved-phase precolumn of 0.3 mm 175 i.d.×5 mm (Dionex) by solvent A delivered by the Switchos 176

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pumping device (LC Packings Dionex), at a flow rate of 10 µL/ 177 min for 3 min. Peptides were then separated on a 75 µm 178i.d.×15 cm C18 Pepmap column (Dionex). The flow rate was 179set at 200 nL/min. Peptides were eluted using a 0% to 35% linear 180 gradient of solvent B (25% H2O/75% ACN/0.1% HCOOH) in 181 80 min then a 35% to 100% linear gradient of solvent B in 182 10 min and finally 100% of solvent B was maintained for 183 184 5 min. Coated electrospray needles were obtained from New 185 Objective (Woburn, Massachusetts, USA). The spray voltage was 1.65 kV. The mass spectrometer was operated in the posi-186 tive ion mode. Data acquisition was performed in a data-187 dependent mode consisting of, alternatively, a full-scan MS 188 over the range m/z 300–2000, and a full-scan MS/MS of the ion 189 selected over the range m/z 50–2000 in an exclusion dynamic 190 mode (the most intense ion is selected and excluded for further 191 selection for a duration of 30 s). MS/MS data were acquired 192using a mass tolerance of 50 mmu and the collision energy 193 was automatically fixed by the device. For the automated data-194base search of fragment ion spectra, the Analyst QS software 195

and Mascot dll script were used and final database searching 196 was performed using Mascot software (Matrix Science London, 197 UK, MS/MS ion search module), in the Swiss-Prot database 198 (Sprot 0411, 525,207 sequences). Search parameters were as fol-199 lows: Rattus as the taxonomic category, 100 ppm tolerance for 200 the parent ion mass and 50 mmu for the MS/MS fragment 201 ions, one missed cleavage allowed, carbamidomethylcysteine 202 as a fixed modification, and methionine oxidation as a possible 203 modification. Only proteins with a significant Mascot score 204 were taken into consideration and reported after manual verifi-205 cation of the fragmentation spectra. 206

#### 2.5. Western blot validation of identified proteins 207

A separate set of animals was used for immunoblotting exper- 208 iments. Four to six animals per group were analyzed in dupli- 209 cate. Rats were killed by decapitation and brains rapidly 210 removed; hippocampi (dorsal and ventral where described) 211 were dissected and stored at -80 °C until homogenization. 212



Fig. 1 – (A) Representative 2D gel image with spots of proteins listed in Table 1 in the 3–10 pH range. (B) Functional clustering of the identified proteins regulated by PRS in the adult hippocampus.

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Tissues were homogenized at 4 °C with a TissueRuptor (Quia-213 gen) in lysis buffer (pH 7.4) containing: 320 mM Sucrose, 5 mM 214 Hepes, 500 mM sodium fluoride, 10% SDS and phosphatase/ 215protease inhibitor (Sigma). BCA assay was used to determine 216 protein concentration. Lysates were resuspended in laemli re-217ducing buffer and 25 µg of each sample was first separated by 218 electrophoresis on 8-12% SDS-polyacrylamide gels and sud-219denly later transferred to nitrocellulose membranes (Biorad). 220221 Transferring was performed at 4 °C in a buffer containing 22235 mM TRIS, 192 mM glycine and 20% methanol.

The following primary antibodies were used to detect the 223relevant proteins: anti-Prohibitin (Thermo Scientific; 1:1000), 224anti-LASP-1 (Millipore; 1:1000), anti-Fascin (Santa Cruz; 1:2000), 225anti-Transferrin (AbCam; 1:5000), anti-β-Actin (Sigma; 1:80000). 226Secondary antibodies directed against rabbit or chicken were 227used at 1:10,000 dilution. Densitometric analysis was performed 228 with Quantity One software (Bio-Rad) associated to a GS-800 229scanner. A ratio of target to B-Actin was determined and these 230values were compared for statistical significance with the Stu-231dent's t-test. 232

#### 233 3. Results

#### 235 3.1. PRS altered the hippocampal proteome

To identify novel proteins modified by PRS we compared the proteome in the hippocampus of adult male PRS and control rats. Analysis of two-dimensional electrophoresis patterns by using Progenesis SameSpots Software revealed that the densities of 24 spots were significantly different (p<0.05) between control and PRS rats.

Among them, 18 spots with a 1.5–3.5 fold change shown on 242 a gel in Fig. 1A, were unambiguously identified as known pro-243teins by nanoLC-tandem mass spectrometry. A total of 26 dif-244ferent identified proteins were thus sorted into the following 5 245groups based on their biological function: (i) signal transduc-246tion; (ii) synaptic vesicles; (iii); protein synthesis (iv) cytoskel-247eton dynamics; and (v) energetic metabolism (Fig. 1B). These 248proteins are listed in Table 1 and Supplemental Table 1. We 249identified up to 6 different proteins per regulated spot in 250251some cases, due to possible overlapping protein spots in the wide pH 3-10 range. The image analysis identified spots 3 252and 9 as being up-regulated by PRS whereas all the other 253spots were found to be down regulated. We could identify 254mainly soluble and cytosolic proteins. It is therefore likely 255that many other changes remained undetected, particularly 256those involving low abundant proteins, or more hydrophobic 257and high molecular weight proteins. 258

#### 259 3.2. Immunoblotting validation of proteomic data

In order to confirm proteomic data in the hippocampus, the 260 261 expression of proteins previously identified within the regu-262lated spot were examined by immunoblot analysis in a separate set of animals (Fig. 2). We found that PRS decreased the 263 expression of Lasp-1 (spot no. 13; F(1,8)=7.73, p<0.05) and in-264creased the expression of transferrin (spot no. 3; F(1,8)= 26510.21, p<0.05), prohibitin (spot no. 9; F(1,8)=13.19, p<0.05), 266 and fascin (spot no. 19; F(1,8) = 6.16, p < 0.05). The increase in 267



Fig. 2 – Immunoblot analysis of fascin, prohibitin, transferrin, and LASP-1 in the hippocampus of control and PRS adult rats. Values are means+S.E.M. of 6 biological replicates. \*p<0.05 vs. controls.

the expression of fascin could appear discordant with the gen-268 eral down regulation profile of spot 19, as revealed by MS/MS 269 analysis. However, fascin accounts for the 30% only of the 270 peptides mixture if we take into account the fifteen different 271 sequences of peptides identified within the spot. The decrease 272 in intensity of spot 19 observed in the comparative analysis of 273 2D-gels may thus come from the other identified candidates. 274

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#### 4. Discussion

This study applied for the first time a proteomic approach to 277 the rat model of PRS that recapitulates some of the features 278 of stress-related disorders in humans [14,15]. This model is 279 valuable for the study of the pathological epigenetic program- 280 ming induced by stressful events occurring early in life (see 281 Introduction and references therein). We found that PRS al- 282 tered the expression profile of several hippocampal proteins, 283 including proteins involved in signal transduction, intracellu- 284 lar trafficking and membrane fusion of synaptic vesicles. In- 285 terestingly, some of the proteins modified by PRS such as 286 synapsin 2, LASP 1 and prohibitin, are known to be glucocorti- 287 coid regulated. This is relevant because PRS rats present an in- 288 creased secretion of glucocorticoid in response to stress [16]. 289 Indeed, inactivation of glucocorticoid receptor in the hippo-290 campus reduces levels of synapsins in mice (2-), and acute 291 corticosterone treatment enhances Lim family proteins [27], 292 among which there is LASP1, a dynamic focal adhesion pro- 293 tein involved in mechanisms of cell migration and survival 294 [28,29]. Prohibitin also was modified by PRS. Such protein is a 295 membrane-bound chaperone which inhibits DNA synthesis 296 and has been implicated in aging, mitochondrial inheritance 297

# Table 1 – Selected list of proteins whose expression was modified in the hippocampus of PRS rats. Proteins were separated by 2D electrophoresis, and nano-LC-MS/MS analysis was performed after trypsin digestion on silver-stained spots. The biological function of the identified proteins is indicated based on gene ontology. Accession number, entry name, and theoretical MW and pI are indicated, according to the UniProtKB database on the Expasy server. For each candidate, the Mascot score and the number of matched peptides obtained from the MS/MS ion Search module (Mascot) are indicated. Spot numbers are reported according to Fig. 1A. <sup>(?)</sup> Synapsin-2 and vesicle-fusing ATPase proteins have been identified in spot nos. 39 and 50 (see Suppl Table 1). The higher score obtained for each of these candidates is reported here.

t1.2 t1.3	Spot	Biological process	Protein name	Entry name	Accession	MW Kda	pI	Mascot score	Peptides
t1.4		Signal transduction							
t1.5	19	-	CaMK2	KCC2A	P11275	54	6.6	62	1
t1.6	13		Phytanoyl CoA hydroxylase interacting protein	PHYYIP	Q568Z9	38	6.5	134	2
t1.7		Synaptic vesicles							
t1.8	39		Synapsin-2 <sup>(*)</sup>	SYN2	Q63537	63	8.73	78	1
t1.9	26		Synaptosomal-associated protein 25	SNAP25	P60881	23	4.66	235	8
t1.10	3		Syntaxin binding protein 1	STXB1	P61765	68	6.49	161	4
t1.11		Protein synthesis							
t1.12	9		Prohibitin	PHB	P67779	29	5.5	191	5
t1.13	50		Elongation factor 1-alpha 1	EF1A1	P62630	50	9.10	67	1
t1.14	19		T-complex protein1 beta subunit	TCPB	Q5XIM9	57	6.01	89	2
t1.15	19		F-box/LRR-repeat protein 16	FXL16	Q5MJ12	52	6.1	147	3
t1.16		Cytoskeleton							
		dynamics							
t1.17	19		Fascin	FSCN_1	P85845	55	5.8	169	5
t1.18	13		LASP-1	LASP1	Q99MZ8	30	6.5	64	2
t1.19	15		Dihydropyriminidase-like2	DPYL2	P47942	62	5.9	321	8
t1.20	24		Guanine nucleotide-binding protein G(olf) subunit alpha	GNAL	P38406	45	6.23	39	1
t1.21	50		Vesicle-fusing ATPase <sup>(*)</sup>	NSF	Q9QUL6	83	6.55	51	3
t1.22	17		Mitochondrial import receptor subunit TOM70	TOM70	Q75Q39	68	7.4	117	3
t1.23		Energetic metabolism							
t1.24	3		Transferrin	TRFE	P12346	78	7.14	121	3
t1.25	10		Phosphomannose isomerase	PMI	Q68FX1	47	5.7	187	4
t1.26	1		6-phosphofructokinase type C	K6PP	P47860	86	6.95	175	5
t1.27	10		Adenosine kinase	ADK	Q64640	40	5.7	66	2
t1.28	29		ATP synthase subunit gamma, mitochondrial	ATPG	P35435	30	8.87	37	2
t1.29	23		Glucose-6-phosphate 1-dehydrogenase	G6PD	P05370	60	5.97	64	3
t1.30	24		Isocitrate dehydrogenase [NAD] subunit alpha	IDH3A	Q99NA5	40	6.47	247	7
t1.31	29		Nitrilase homolog 2	NIT2	Q497B0	31	6.9	41	2
t1.32	20		Pyruvate kinase isozymes M1/M2	KPYM	P11980	58	6.63	521	18
t1.33	19		Succinate-semialdehyde-deydrogenase	SSDH	P51650	56	8.3	97	2
t1.34	19		Tryptophanyl-tRNA-ligase	SYWC	Q6P7B0	54	6.0	145	2

and apoptosis (for review see Ref. 30). The increment of prohi-298 299bitin induced by PRS is in line with other reports about increased probitin levels after glucocorticoids exposure during 300 early postnatal life such as maternal separation [31] or chronic 301 stress (restraint) in adult life [32]. Thus, we provide the first 302 evidence that in utero exposure to stress persistently affects 303 the expression in the hippocampus of proteins from different 304functional categories, which are known to be regulated by 305stress and/or glucocorticoids. This observation underlines 306 the putative involvement of the early exposure to glucocorti-307308 coids in the permanent modification of the hippocampal proteome in the PRS model. 309

PRS also increased expression of Fascin, an actin-bundling 310 protein that lies downstream of the GTP-binding protein, 311 312 Rab35, in the regulation of cytoskeleton dynamics and formation of filopodia and growth cones [33,34]. The fascin-313 314 encoding gene, FSCN1, is positively regulated by CREB and is 315 induced during neuronal differentiation of NT2 precursor cells [35]. In addition, fascin is up-regulated in neuroectoder-316 317mal spheres derived from human embryonic stem cells, and is highly expressed in the subventricular zone of the fetal 318 mouse brain [36]. These data suggest that fascin coordinates 319 cytoskeletal changes associated with neuronal differentia- 320 tion, although the precise role of this protein in the adult hip- 321 pocampal neurogenesis remains to be determined. PRS rats 322 showed an increased expression of fascin in spite of the ob-323 served reduction of phospho-CREB levels and neurogenesis 324 in the hippocampus [18,20,23]. In contrast, fascin is down-325 regulated in the ventral hippocampus of normal rats treated 326 with the antidepressant, escitalopram [30]. Perhaps fascin 327 acts as a negative regulator of adult neurogenesis and anti-328 depressants enhance neurogenesis by reducing the expres-329 sion of fascin. This interesting hypothesis warrants further 330 investigation. 331

A number of proteins involved in cellular metabolism were 332 modified by PRS. One example was phosphomannose isomerase, 333 a key enzyme in the biosynthetic pathway of N-glycosylprotein 334 [37]. Protein glycosylation critically regulates different aspects of 335 neuronal function including synaptic plasticity [38], and has 336 been implicated in the pathophysiology of neurodegenerative 337

Please cite this article as: Mairesse J, et al, Proteomic characterization in the hippocampus of prenatally stressed rats, J Prot (2012), doi:10.1016/j.jprot.2011.12.017

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IOURNAL OF PROTEOMICS XX (2012) XXX-XXX

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disorders [39,40]. However, inactivating mutations of phospho-338 mannose isomerase causes the congenital disorder of glycosyla-339 tion type Ib, in which the CNS is not affected [41,42]. Thus, the 340 precise relationship between phosphomannose isomerase and 341 the pathological phenotype of PRS rats remains to be determined. 342 Other identified proteins were 6-phosphofructokinase, pyruvate 343 kinase and glucose-6-phosphate dehydrogenase, three enzymes 344 involved in glucose utilization and energetic metabolism that are 345 346 activated by insulin [43,44]. Changes in the expression of the three enzymes could contribute to the development of insulin re-347 sistance and altered glucose metabolism seen in PRS rats [45,46]. 348 A decreased energetic metabolism is expected in light of the de-349pressive phenotype and the negative resilience to stress exhib-350ited by PRS rats [14,15,47]. 351

In conclusion, our data offer the first evidence that PRS in-352duces long-lasting changes in the expression profile of hippo-353 campal proteins that likely reflect a pathological epigenetic 354program triggered in the perinatal life. Anxiety generated by 355 restraint stress in pregnant mothers [48] might influence 356 brain development during the fetal life as a result of malnutri-357 tion or excessive exposure to maternal corticosteroids [49]. Al-358 ternatively, the epigenetic misprogramming of PRS rats can be 359 the consequence of the low maternal care in the first week of 360 361 postnatal life induced by gestational stress (personal observa-362 tions from the laboratory). The latter hypothesis is more likely 363 because there is compelling evidence that low maternal care 364 causes permanent changes in gene function and behavior in the offspring [2,7,50], and cross-fostering, which increased 365 maternal care, prevents at least the abnormal HPA response 366 to stress induced by PRS in particular on MR and GR hippo-367 campal receptors [16]. Changes in hippocampal proteins 368 seen in PRS rats may facilitate the identification of novel mo-369 lecular processes and candidate genes involved in the regula-370 tion of the stress response and in the pathophysiology of 371 mood disorders. 372

5. **Uncited** reference O2374

375 [26]

#### Acknowledgements 376

This study was supported by North University of Lille (Lille 1) 378 and the Sapienza University of Rome (Frame Agreement 379 signed between the two universities on 15/02/2007) and by 380 CNRS in the framework of the European Research Team 381 (GDRE 691) "Early Programming of Modern Diseases" We 382 thank AS Lacoste and Dr C. Rolando of the Centre Commun 383 384 de Mesure de Spectrométrie de Masse (North University of 385 Lille) for mass spectrometry analyses. English editing services 386 were provided by Gap Junction (www.gap-junction.com).

#### Appendix A. Supplementary data 388

389 Supplementary data to this article can be found online at doi:10.1016/j.jprot.2011.12.017. 390

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Please cite this article as: Mairesse J, et al, Proteomic characterization in the hippocampus of prenatally stressed rats, J Prot (2012), doi:10.1016/j.jprot.2011.12.017

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IOURNAL OF PROTEOMICS XX (2012) XXX-XXX

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