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1 Tachykinins, new players in the control of reproduction and
2 food intake: a comparative review in mammals and teleosts
3

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13

14 Running title: Tachykinin system, reproduction and feeding in mammals and teleosts

15 **Abstract**

16 In vertebrates, the tachykinin system includes tachykinin genes, which encode one or two
17 peptides each, and tachykinin receptors. The complexity of this system is reinforced by the
18 massive conservation of gene duplicates after the whole genome duplication events that
19 occurred in vertebrates and furthermore in teleosts. Added to this, the expression of the
20 tachykinin system is more widespread than first thought, being found beyond brain and gut. The
21 discovery of the co-expression of neurokinin B, encoded by tachykinin 3 gene, and
22 kisspeptin/dynorphin in neurons involved in the generation of GnRH pulse in mammals, put a
23 spotlight on the tachykinin system in vertebrate reproductive physiology. As food intake and
24 reproduction are linked processes, and considering that hypothalamic hormones classically
25 involved in the control of reproduction are reported to regulate also appetite and energy
26 homeostasis, it is of interest to look at the potential involvement of tachykinins in these two
27 major physiological functions. The purpose of this review is thus to provide first a general
28 overview of the tachykinin system in mammals and teleosts, before giving a state-of-the-art on
29 the different levels of action of tachykinins in the control of reproduction and food intake. This
30 work has been conducted with a comparative point-of-view, highlighting the major similarities
31 and differences of tachykinin systems and actions between mammals and teleosts.

32

33

34 Introduction

35 Tachykinins (TAC) are members of a large family of peptides present from cnidaria [for reviews:
36 (1,2) to bilateria [for reviews: (1–8). Tachykinins are usually considered as brain and gut
37 peptides, as they are mainly expressed in neurons from the central nervous system and from the
38 gastrointestinal tract. However, they are also present in non-neuronal cells, such as the immune
39 and inflammatory cells of mammals, and various tissues like the skin of amphibians, as well as
40 the salivary gland of mosquito and octopus, where they serve as exocrine secretion [for reviews:
41 (1,4,6,8)]. In addition, in sea squirt, they are found in endostyle and gonad (8), where they act as
42 neurotransmitters of endocrine and local autocrine/paracrine regulations [for reviews: (4,8)].

43 Since the discovery of the co-expression of neurokinin B, encoded by tachykinin 3 gene (*tac3*),
44 and kisspeptin/dynorphin in neurons involved in the generation of GnRH pulses in mammals,
45 rekindled attention emerged for studying tachykinins in vertebrate reproductive physiology.
46 Reproduction is classically controlled by the hypothalamus-pituitary-gonad (HPG)
47 neuroendocrine axis in vertebrates [for review: (9)]. Gonadotropin-releasing hormone (GnRH),
48 produced and released by hypothalamic neurons, acts on the pituitary to stimulate the synthesis
49 and release of gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
50 These pituitary hormones act themselves on the gonads to control gametogenesis and the
51 production of sex steroids, mainly estrogens in females and androgens in males. These
52 peripheral hormones exert feedbacks at brain and pituitary levels to regulate GnRH and
53 gonadotropin production. Hypothalamus is also the cerebral center involved in the control of
54 food intake, integrating both external and internal factors, and producing neuropeptides
55 stimulating (orexigenic) or inhibiting (anorexigenic) appetite [for reviews: (10–13)].

56 In vertebrates, feeding and reproduction are linked processes, as the presence of sufficient
57 energy reserves is critical to achieve successful reproduction [for reviews: (14,15)]. Any state of
58 negative energy balance thus not only affects central appetite regulating systems but, often,
59 also reproductive pathways and reproductive performance. Hypothalamic hormones classically
60 involved in the control of reproduction, such as kisspeptin, are reported to regulate appetite and
61 energy homeostasis as well, in mammals [for reviews: (16–18)] and teleosts [for review: (19)].

62 As teleosts represent the most diversified group of vertebrates, with nearly 30,000 species,
63 species-specific regulating mechanisms are often encountered inside this lineage. In addition,
64 some physiological differences exist between fish and mammalian regulatory mechanisms, even
65 if major regulatory features are conserved. Some differences may be due to anatomical
66 specificities of teleost neuroendocrine systems such as direct neuronal innervation and cell
67 regionalization of the pituitary [for reviews: (9,20)]. Major breakthroughs in the studies of
68 neuropeptide actions in teleosts have been allowed thanks to recently available published
69 genomes and novel genome editing technics. These new tools are of particular interest and
70 necessity in this group of vertebrates, as due to the teleost specific whole genome duplication
71 (3R), teleosts possess expanded number of genes encoding hormones/peptides that will share
72 initial pleiotropic functions (subfunctionalization) or get new functions (neofunctionalization)
73 [for review: (9)].

74 With a comparative perspective, the purpose of this review is to provide a general overview of
75 the tachykinins and their receptors in mammals and teleosts, and then focus on the state-of-
76 the-art literature on the different levels of action of tachykinins in the control of reproduction
77 and food intake in these two groups of vertebrates.

78

79 **1. Tachykinin system**

80 Some of the first peptides of the tachykinin (TAC) family were discovered in neurons in
81 mammals, and therefore named neurokinins (NK). However, many subsequent data showed
82 their production by non-neuronal cells. Especially the discovery in 2000 by Zhang and
83 collaborators of a third tachykinin gene, PPT-C (21), renamed *tac4* and encoding several new
84 tachykinin peptides, with widespread peripheral distributions and with preferred receptor NK1
85 receptor, led to debates on their nomenclature [for reviews: (22,23)]. A revised nomenclature
86 was proposed, with the preferred term ‘tachykinin’ compared to ‘neurokinin’, which then
87 appeared inappropriate. Similarly, for tachykinin receptors, for example, NK1 receptor can no
88 longer be defined only as substance P (SP) receptor [for reviews: (23,24)]. More recently, the
89 Human Genome Organization (HUGO) Gene Nomenclature Committee approved the names
90 TACR1, TACR2 and TACR3 for the three TAC receptors (25). This nomenclature will be adopted in
91 our review. In the following text, we will use TAC for tachykinin peptides and *tac* for tachykinin
92 genes and transcripts, and likewise TACR and *tacr* for the receptors.

93 A recent review highlights the widespread distribution and the functional pleiotropy of TACs and
94 their receptors with a special focus on invertebrates (2), and is complementary to our present
95 comparative review in vertebrates.

96 **1.1. Tachykinins**

97 The evolutionary scenario of tachykinins in chordates suggests that an ancestral *tac* gene in
98 proto-chordates generated four paralogs [(26), for reviews: (1,27)] after the two whole genome
99 duplication rounds (1R/2R) which occurred in early vertebrates (28,29). A possible loss of one of
100 the four paralogs occurred before the split of the ray-finned fish, actinopterygians (leading to
101 teleost fish) and the lobe-finned fish, sarcopterygians (leading to mammals) [(26), for review:
102 (1)]. Among teleosts, a specific third genome duplication (3R) produced a tetraploidization,
103 followed by gene loss or conservation of duplicated paralogs (30,31). Our recent study shows a
104 wide conservation of the duplicated tachykinin genes in the teleost fish lineage (Campo et al. in
105 preparation), thus increasing the scope of previous research (26).

106 Vertebrate *tac* genes consist in five to seven exons that encode a pre-pro-tachykinin (PPT)
107 peptide, named PPT-A or PPT-I for *tac1*, PPT-B or PPT-II for *tac3* and PPT-C or PPT-III for *tac4* [for
108 reviews: (4,32–34)]. One or two peptides are cleaved from each of the three PPT [for reviews:
109 (1)]. The TAC peptide placed close to the N-terminal of PPT is called TAC-related peptide or
110 TACRP, while the other tachykinin peptide closer to the C-terminal of PPT is named TAC. For
111 *tac1* gene, TACRP is substance P (SP) and TAC are neurokinin A (NKA), neuropeptide K (NPK) and
112 neuropeptide γ (NP γ), these last two being NH₂-terminally extended forms of NKA. For *tac3*
113 gene, TACRP (only found in teleosts) is TAC3RP or neurokinin B-related peptide (NKBRP), and
114 TAC is NKB. For *tac4* gene, TACRP are hemokinin-1 (HK1), endokinin A (EKA) and endokinin B
115 (EKB), while TAC are endokinin C (EKC) and endokinin D (EKD), depending on the splicing variant
116 (Figure 1). Indeed in mammals, differential alternative mRNA splicing and precursor processing
117 are observed for each of the three tachykinin genes, and as the different transcripts are
118 regulated in a tissue-specific manner [*tac1*: (35–37); *tac3*: (38); *tac4*: (39); for reviews: (40,41)],
119 these mechanisms are likely to play an important role in the pleiotropic actions of the various
120 tachykinins.

121 TAC are characterized by a FxGLMamide carboxy-terminus, where x is a variable, aromatic or
122 aliphatic, amino acid [for review: (5)]. Some exceptions are found: for example, the human EKC
123 and EKD present a substitution of the final M by L (42,43). For NKA and NKB, as well as the
124 extended forms of NKA (NPK and NP γ), x is always a Valine, leading to a FVGLM C-terminal motif
125 (44).

126 **1.1.1. Tachykinin 1**

127 **1.1.1.1. Mammals**

128 Four peptides can be translated from the gene *tac1* (Figure 1): substance P (SP) or TAC1RP from
129 exon 3; neurokinin A (NKA) or TAC1 from exon 6; neuropeptide K (NPK) or TAC1-NPK from exons
130 4, 5 and 6; and neuropeptide gamma (NP γ) or TAC1- NP γ from exons 3, 5 and 6 [for reviews:
131 (34,45)]. The *tac1* gene produces four different splicing variants (α -, β -, γ -, and δ -*tac1*): α - and δ -
132 *tac1* generate only SP; β -*tac1* encodes SP, NKA and NPK; γ -*tac1* generates SP, NKA and NP γ [for
133 reviews: (34,45,46)]. Substance P/TAC1RP was the first neuropeptide ever to be extracted in
134 1931 [(47); for review: (48)]. In their pioneer study, von Euler and Gaddum found in extracts
135 from horse brain and intestine, an atropine-resistant factor, which induced contraction of
136 isolated rabbit jejunum and transient hypotension in anesthetized rabbits (47). They named this
137 new factor, substance P, with P for Powder. It was only in 1971 that SP was purified and
138 sequenced from bovine hypothalamus (49), and synthesised (50). Neurokinin A/TAC1 was
139 discovered later in extracts of porcine spinal cord by different research groups and named
140 differently at that time: neurokinin α (51), substance K (52) or neuromedin L (53). As SP, it was
141 involved in ileum contraction of guinea pig (51,53). Further analyses of the pre-pro-peptide
142 structure revealed that other peptides than SP and NKA were encoded by the precursor and that
143 tissue-specific alternative splicing occurred (35,52): neuropeptide K (NPK) with 36 amino-acids
144 and neuropeptide gamma (NP γ) with 21 amino-acids. Both sequences share the last 10 amino-
145 acids in the C-terminal with NKA/TAC1 sequence. NPK, isolated from porcine brain, stimulates
146 guinea-pig gallbladder contraction, plasma extravasation, hypotension and bronchial smooth
147 muscle spasm (54). NP γ was isolated from rabbit intestine and found to derive from γ -pre-pro-
148 tachykinin, hence its name (55).

149 **1.1.1.2. Teleosts**

150 The first TAC peptide to be characterized in teleosts was substance P. In 1956, a factor purified
151 from cod brain and intestine extracts was found to have the same properties as mammalian
152 substance P (56). Later, a tachykinin of 21 amino acid residues, which possesses mammalian NP γ
153 characteristics and was named carassin, was isolated from the brain of the goldfish *Carassius*
154 *auratus* (57). Then, SP and NKA were measured by radioimmunoassay in the brain of rainbow
155 trout (58). In goldfish, Lin and Peter described two cDNAs encoding γ -PPT that may represent
156 different transcripts resulting from the alternative transcriptional start sites and that contains
157 the sequences of SP, carassin and NKA (59). *Tac1* gene was first characterized in zebrafish and
158 found in the genomes of goldfish, medaka and stickleback; it encodes SP and NKA (60,61). One
159 *tac1* gene was then found in many other teleost species, including grass carp (62). It was only
160 recently that a second *tac1* gene, likely the result of the 3R, was identified in the grass carp; the
161 duplicated genes were named *tac1a* and *tac1b* and shown to encode SPa and NKAa, and SPb
162 and NKAb, respectively (63) (Figure 1). Before that study, it was thought that one of the
163 duplicated *tac1* paralogs obtained by 3R was lost in teleosts [for review: (1)]. Our recent
164 bioinformatic studies revealed a wide conservation of the 3R-duplicated *tac1* genes, even those

165 obtained by the further whole genome duplication of the salmonids (4R) (Campo et al. in
166 preparation).

167 **1.1.2. Tachykinin 3**

168 **1.1.2.1. Mammals**

169 *Tac3* gene has been named *tac2* in rodents, while it is in fact an ortholog of human *tac3* (45,64–
170 67): so for easier reading, rodent *tac2* will be replaced by *tac3* throughout this review. One
171 peptide is encoded in the *tac3* gene: neurokinin B (NKB) or TAC3 (32,38,41,45). NKB was purified
172 from the extract of porcine spinal cord simultaneously by two research groups and given
173 different names at that time: neurokinin β (51) or neuromedin K (68). As SP and NKA, it induces
174 contraction of the guinea pig ileum (51,68). The structure and the gene organization of
175 neuromedin K/NKB precursor (or pre-pro-tachykinin B) was first determined in bovine (69), then
176 in rat (70). In human, a single gene transcript encoding a single precursor and a single TAC was
177 first revealed (71), but then three TAC3 precursors (α , β and γ) were shown to exist (Figure 1)
178 (38).

179 **1.1.2.2. Teleosts**

180 The *tac3* gene has been characterized in a number of teleost species: zebrafish *Danio rerio*
181 (26,61,72), Nile tilapia *Oreochromis niloticus* (73), goldfish *Carassius auratus* (74), striped bass
182 *Morone saxatilis* (75), grass carp *Ctenopharyngodon idellus* (63,76), European eel *Anguilla*
183 *anguilla* (77), orange-spotted grouper *Epinephelus coioides* (78), spotted sea bass *Lateolabrax*
184 *maculatus* (79) and half-smooth tongue sole *Cynoglossus semilaevis* (80). While the *tac3* gene
185 codes for only one TAC3 peptide in mammals, its ortholog in teleosts codes for two putative
186 tachykinin peptides, TAC3 and a TAC3 related peptide [TAC3RP or NKBRP: (77,78)], earlier
187 named neurokinin F (NKF) (72) with ‘F’ for ‘fish’ as it was thought to be present only in fish
188 species and preserved along the whole teleost radiation (72,73). As the whole genome
189 duplication event specific to the teleost lineage (3R) led to the duplication of the *tac3* gene into
190 *tac3a* and *tac3b*, up to four neurokinin B peptides may exist in teleosts, namely NKBRPa, NKBa,
191 NKBRPb and NKBb (Figure 1). Loss of *tac3b* is observed in orange-spotted grouper (78), tongue
192 sole (80), striped bass *Morone saxatilis* (75), olive flounder *Paralichthys olivaceus*, tiger puffer
193 *Tetraodon nigroviridis*, medaka *Oryzias latipes*, Atlantic herring *Clupea harengus*, alosa *Alosa*
194 *alosa*, rainbow smelt *Osmerus mordax* and sheepshead minnow *Cyprinodon variagatus* (77),
195 leading to the presence of only two peptides in these species (Campo et al. in preparation).

196 **1.1.3. Tachykinin 4**

197 **1.1.3.1. Mammals**

198 The molecular cloning of a mouse third PPT gene, PPT-C (later renamed *tac4*), was reported in
199 2000 (21). PPT-C mRNA was primarily detected in hematopoietic cells and its derived peptide
200 was shown to be crucial factor for the survival of B cell precursors and thus named hemokinin 1
201 [HK1; (21)]. Rat HK1 is identical to mouse HK1 (mHK1) (81). In human, the *tac4* transcript
202 predicts two tachykinin-like peptides: one, at N terminus, homolog of mouse and rat HK1, was
203 named endokinin A (HK1/EKA), and the second at C terminus was named endokinin C (EKC), in
204 line with their proposed peripheral endocrine roles in contrast to the neuroendocrine/neuronal
205 role of neurokinins (39). Apart from this *tac4* transcript that was named α -*tac4*, three other
206 splicing variants exist in human (β -, γ -, and δ -*tac4*) (Figure 1): β -*tac4* codes for EKB and EKD,

207 while γ -*tac4* and δ -*tac4* encode only EKB [(39); for review: (67)]. TAC4RP-EKA and TAC4RP-EKB
208 are N-terminal extended version of TAC4RP-HK1, with different lengths, EKB is a truncated form
209 of EKA and EKD a N-terminally modified version of EKC (39). Thus, the *tac4* gene encodes up to
210 five peptides in mammals: HK1, EKA, EKB, EKC and EKD. Three of them can be translated from
211 the TAC4-RP and two from the TAC4 site: HK1 or TAC4RP-HK1 from exon 2; EKA or TAC4RP-EKA
212 from exons 1 and 2; EKB or TAC4RP-EKB from exons 1 and 2; EKC or TAC4-EKC from exons 3 and
213 4; and EKD or TAC4-EKD from exon 4; EKC and EKD are designated tachykinin gene related
214 peptides [for reviews: (34,40,45,67)]. Interestingly, TAC4-EKC and TAC4-EKD that correspond to
215 the TAC4 peptide have substituted the C-terminal methionine by a lysine thus reducing or
216 suppressing the affinity for all TAC-receptors, and differ by the length of the N-terminus (39).

217 **1.1.3.2. Teleosts**

218 It was not clear whether homologs of HK and EK were present in non-mammalian vertebrates
219 until *tac4* gene was identified in the genomes of various teleosts (72), and recently
220 characterised in brain grass carp (63). Grass carp *tac4* gene encodes two mature peptides,
221 hemokinin 1 (HK1) and hemokinin 2 (HK2) (Figure 1), as the mammalian *tac4*. However, the
222 mammalian *tac4* can produce up to four different peptides depending on alternative splicing
223 events that have not been observed in teleosts until now. HK-1 displays very weak activation for
224 neurokinin receptors compared to HK2, likely due to a phenylalanine to valine substitution in
225 the C-terminal FXGLM signature motif, and leading to an inefficiency on pituitary hormone
226 expression in grass carp pituitary cells (63). Shi and colleagues proposed that the fact that only
227 one TAC4 isoform was isolated up to now in teleosts 'might be the result of the non-
228 functionalization by forming pseudogenes or deletion/mutations leading to the loss of
229 redundant genes' (63). Our recent study demonstrates that the *tac4* gene has been duplicated
230 during the 3R and two copies of the gene were conserved in most studied species (Campo et al.
231 in preparation) (Figure 1).

232 **1.2. Tachykinin receptors**

233 In vertebrates, TAC peptides bind to three receptors (TACR), belonging to the first-class
234 rhodopsin-like G-protein coupled receptors (GPCR) (also named as family A GPCRs): TACR1,
235 TACR2 and TACR3. These receptors are normally encoded by five exons that include the seven
236 transmembrane domains, an extracellular N-terminus enrolled in peptide recognition, and an
237 intracellular C-terminal end in charge of the cellular response after activation of the receptor
238 [for reviews: (34,82)].

239 The evolutionary scenario of tachykinin receptors in chordates (26) suggests that an ancestral
240 tac receptor (*tacr*) gene in protochordates generated four paralogs after 1R/2R in early
241 vertebrates (28,29). One *tacr*, the *tacr4* gene, would have been lost before the split of the
242 actinopterygians (ray-finned fish) and the sarcopterygians (lobe-finned fish). Further duplication
243 of the *tacr* genes occurred during the teleost 3R. The 3R-duplicated *tacr1* and *tacr3* genes
244 are conserved in most teleosts (Campo et al. in preparation), while one of the 3R-
245 duplicated *tacr2* paralog (*tacr2b*) was subsequently lost in the teleost lineage but conserved in
246 the eels (elopomorphs) (Campo et al. in preparation). A local duplication of *tacr3a* might have
247 occurred to give rise to *tacr3a1* and *tacr3a2* genes in the teleost lineage (26) Our recent gene
248 search and phylogenetic study confirms this local duplication, but only in the clupeocephala, not

249 in elopomorphs (*Anguilla* species) nor osteoglossomorphs (bony tongue) (Campo et al. in
250 preparation).

251 **1.2.1. Tachykinin receptors in mammals**

252 Nakanishi group first demonstrated, by electrophysiological measurements of *Xenopus* oocytes
253 injected with brain and stomach mRNAs, the expression of the receptors for mammalian SP
254 (named NK1 receptor, here TACR1) and NKA (named NK2 receptor, here TACR2), respectively
255 (83). The same year, the receptor for bovine NKA (TACR2), was cloned from bovine stomach
256 (84). The receptors for substance P, TACR1 (85), and for NKB, TACR3 (86), were then cloned
257 from rat brain. When expressed in *Xenopus* oocytes and in COS cells, they can produce
258 electrophysiological response as follows: SP>NKA>NKB for TACR1; NKA>NKB>SP for TACR2, and
259 NKB>NKA>SP for TACR3 (Figure 1) [for review: (34)]. Thus, the three tachykinin receptors can
260 bind all TAC peptides (except EKC and EKD) but with differential selectivity (82,87–89). HK1 and
261 EKs (EKA and EKB) exhibit the highest affinity to TACR1 (Figure 1) [for reviews: (8,34)].

262 **1.2.2. Tachykinin receptors in teleosts**

263 Up to six tachykinin receptors have been characterized in teleosts (Figure 1), results of both
264 whole genome duplication and local gene duplication. In zebrafish, two 3R-duplicated *tacr1*
265 (*tacr1a* and *tacr1b*), one *tacr2* and three *tacr3* (*tacr3a1*, *tacr3a2* and *tacr3b*) are identified, with
266 *tacr3a2* arising from a local duplication of *tacr3a1* (26). In the grass carp, the same receptors are
267 found: duplicated *tacr1* (NK1Ra and NK1Rb in the article), single *tacr2* (NK2R in the article), and
268 three *tacr3* (NK3Ra1, NK3Ra2 and NK3Rb in the article) (63).

269 Using COS-7 cells that expressed zebrafish TACR3a1 (Tac3ra in the article) or zebrafish TACR3a2
270 (Tac3rb in the article), Biran and collaborators reported that both zebrafish NKBa and NKBRP
271 (NKF in the article) were endogenous ligands of TACR3, while zebrafish NKBb was less effective
272 (72). The same year, a local duplication of *tacr3a* was reported in zebrafish and binding studies
273 of the three zebrafish TACR3 (TACR3a1, TACR3a2 and TACR3b) were investigated. NKBRPa
274 (NKBa-13 in the article) and NKBRPb (NKBb-13 in the article) have higher potencies for inducing
275 promoter activity of TACR3a1 and TACR3a2 in both CRE and SRE transactivation assays than
276 NKBa-10 (26). For TACR3b, the same three NKB peptides have inducing effect only using SRE
277 promoter (26). Zebrafish NKBb (NKBb-11 in the article) cannot activate any of the three TACR3s
278 (26). In the same system, tilapia NKBRP (NKF in the article) was more effective than tilapia NKB
279 in inducing the activity of tilapia TACR3a (Tac3ra in the article), and tilapia TACR3b (Tac3rb in the
280 article) (73). In transfected 293-T cells, goldfish NKBa (NKBa-10 in the article), NKBRPa (NKBa-13
281 in the article), NKBb (NKBb-11 in the article) and NKBRPb (NKBb-13 in the article) can activate
282 TACR3a1 (Tac3ra in the article), while TACR3b (Tac3rb in the article) can be slightly activated
283 only by NKBa-10 (90).

284 In the grass carp, three studies investigated the receptor selectivity of TAC peptides, using
285 HEK293T cells transfected with each of the 6 TACRs identified in this species (62,63,91) (Figure
286 1). The first two articles were reported before the cloning of *tac4* gene and thus did not include
287 TAC4 peptides (62,91). The authors found that for TACR1 activation, the potencies were grass
288 carp SP>NKA>NKBa>NKBRPa>NKBRPb>NKBb, and for TACR2 activation, grass carp SP, NKA,
289 NKBa, NKBRPa and NKBRPb had similar potency, except for NKBb which showed a low potency
290 (62). This reveals that carp TACR2 is a multiligand receptor, which could be activated by various
291 TACs with comparable efficacy and potency. Concerning TACR3 activation, for both TACR3a2
292 (NK3Ra in the article) and TACR3b (NK3Rb in the article), grass carp NKBRPb, NKBa and NKBRPa

293 were found to be the most effective compared to NKA, SP and NKBB (91). Interestingly, in the
294 third publication, HK2, product of *tac4* gene, was shown to be able to activate all 6 TACRs, but
295 with the highest activity for TACR2 (TACR2>TACR3b>TACR1a≈TACR3a1≈TACR1B>TACR3a2),
296 while HK1 displays a very weak activation for each of TACR isoforms (63). These results suggest
297 that while mammalian hemokinin HK1 exhibits highest affinity for TACR1, teleost HK2
298 preferentially stimulates the multiligand receptor TACR2, and may thus have similar function as
299 other tachykinins through its activation (63).

300

301 **2. Physiological role of tachykinins in the regulation of reproduction**

302 Activation of gonadotropic axis at puberty onset and maintenance of reproductive state (with
303 generation of GnRH pulse in mammals) are under a complex regulatory network. A major
304 breakthrough occurred in 2003 for reproductive neuroendocrinology with the description of
305 hypogonadotropic hypogonadism in human and mice bearing mutation in either kisspeptin gene
306 (*kiss*) or its receptor (*kissr*) (92–94) and the following multiple evidences that kisspeptins were
307 the most potent secretagogues of GnRH in all mammals [for reviews: (95–97)]. In addition, the
308 involved kisspeptin neurons of the arcuate nucleus (ARC) in the hypothalamus were shown to
309 coexpress neurokinin B and dynorphin and thus referred to as KNDy neurons, first in sheep (98),
310 then in a variety of mammals [for review: (99)]. A model was proposed in mammals for the
311 GnRH pulse generator with NKB stimulating kisspeptin release and dynorphin inhibiting it [for
312 reviews: (100–103)]. All these data rekindle attention to other tachykinins, namely SP and NKA,
313 in reproductive physiology. In contrast, little is known concerning a potential involvement of
314 tachykinin peptides derived from *tac4* gene, hemokinin and endokinins, in the control of
315 reproduction, but potential actions at peripheral level are observed (Figure 2).

316 Some redundancies among the three TACR signalling pathways in the control of reproduction
317 may occur (at least in rodents) as blockade of all three receptors (by the use of an antagonist for
318 all three receptors) is required to inhibit LH secretion [ovariectomized (OVX) rat: (104)], and the
319 *in vitro* stimulatory effect of NKB on KNDy neurons is blocked only in presence of a cocktail of all
320 three receptor antagonists [male mouse: (105)]. In both studies, the use of specific receptor
321 antagonists individually has no effect (104,105).

322 **2.1. At the central level of the HPG axis**

323 The main central targets of tachykinins on the HPG axis are brain gonadotropin-releasing
324 hormone (GnRH) and pituitary gonadotropins (LH and FSH). A recent review deals with the latest
325 advances in our understanding of the biology of tachykinins in the control of GnRH release in
326 mammals (106). However, as HPG axis is also controlled by dopamine (DA) in teleosts,
327 amphibians and seasonal mammals, future studies should aim at investigating the potential
328 regulation of dopaminergic neurons by the products of tachykinin genes. Indeed, in mammals,
329 reports have shown interactions between tachykinins and DA at the hypothalamic level [for
330 review: (107)]. For example, Billings and colleagues demonstrated the presence of TACR3 in DA
331 neurons in the ewe, abundantly during anestrus when DA mediates the suppression of GnRH
332 and LH release, and considerably less during breeding season (108).

333 **2.1.1. TAC1 peptides**

334 **2.1.1.1. Inactivation of TAC1 system and reproduction**

335 To date, in humans, hypogonadotropic hypogonadism has never been associated with mutation
336 of either *tac1* gene or *tacr1/tacr2* genes. However, in mice, inactivation of these different genes
337 leads to different degrees of reproductive impairments, suggesting the need for the whole
338 tachykinin system to get full reproduction. Knockout of *tac1* gene was obtained in female (109)
339 and male (110) mice, which induced a delay in the onset of puberty in both sexes plus a
340 subfertility in female (109). In contrast, mutant mice for *tacr1* are fertile (111). More recently,
341 the characterization of a novel mouse line with congenital ablation of *tacr2* allowed to show
342 partially suppressed basal and stimulated-LH secretion, with moderate reproductive impact
343 (normal puberty onset and fertility), in these null mice (112). However, in the same species,
344 impairment of TAC1 peptide action does not seem to impact reproduction, as when TACR1 or
345 TACR2 antagonists are ip injected to 8-week-old or subcutaneously (sc) to 6-month-old female
346 mice, no effect is observed on reproductive success or litter size (113).

347 **2.1.1.2. Effects of TAC1 peptides on GnRH expression, synthesis and release**

348 **2.1.1.2.1. Mammals**

349 Before the description of KNDy neuron involvement in GnRH pulse generation, and the renewed
350 interest in SP and NKA as regulators of the HPG, few studies were available for a potential direct
351 effect of TAC1 peptides on GnRH [for review: (99)]. Using a perfusion system, Ohtsuka and
352 collaborators (114) were the first to show that SP stimulated the *in vitro* release of GnRH by rat
353 medio-basal hypothalamus (Figure 2). Consistent with this direct action of SP on GnRH in
354 rodents, its receptor, TACR1, was shown to be expressed in a fourth of GnRH neurons in the
355 mice (115), and binding sites for SP detected in the rat hypothalamus (116). In addition, SP
356 neurons establish inputs to GnRH neurons in the rat septo-optic area (117) as well as in
357 human diencephalon (118) and eminence median (119). In contrast, in another mammal, the
358 ewe, no coexpression of SP or TACR1 was detected in GnRH neurons, implying no possible direct
359 effect of SP on GnRH in this species (120). None of GnRH neurons express TACR2 in mouse (115)
360 and no detection of NKA binding sites was observed in the hypothalamus of rat (116), suggesting
361 a lack of potential direct effect of NKA on GnRH in both species. However, Sahu and Kalra
362 reported in female rat that TACR2 agonist, but not TACR1 one, could suppress GnRH release by
363 fragments of median eminence and arcuate nucleus in culture (121).

364 Apart from a potential direct action of SP and NKA on GnRH neurons via their respective
365 receptors, data in mammals report effects on kisspeptin neurons, as for NKB in KNDy network.
366 Stimulatory action of TAC1 peptides on kisspeptin has been demonstrated in rodents. In mice,
367 SP and NKA modulate Kiss1 neurons and kisspeptin release [SP and NKA, males (105); SP and
368 NKA, males and ovariectomized and supplemented with E2 (OVX+E2) females (115); SP, females
369 (109); NKA, females (122)]. SP and NKA are also able to depolarize Kiss1 neurons in male mice
370 (105). In addition, the induction of GnRH release by icv infusion of a SP agonist in adult male and
371 OVX+E2 mice is not observed in Kiss1^{r-/-} mice (115). These results on the kisspeptin-dependent
372 effect of SP on GnRH are consistent with the fact that half of kiss1 neurons express *tacr1* in this
373 species (115). In rat, icv injection of SP elevates both *gnrh* and *kiss1* mRNA levels (123).

374 In other mammalian species, anatomical data suggest possible action of TAC1 peptides on
375 kisspeptin or GnRH, but *in vivo* studies are often lacking or report only limited action. In
376 postmenopausal women, SP immunoreactivity is detected within Kiss1 neurons in infundibular
377 nucleus (124) and Kiss-SP occasionally contact with GnRH in the postinfundibular eminence
378 (119). However, to our knowledge, no *in vivo* data for SP or NKA action on GnRH via kisspeptin

379 are yet available in humans. In the goat, SP fibers are also observed in close apposition within
380 ARC KNDy (125), and high doses of TACR1 and TACR2 agonists are needed, and not effective in
381 all individuals, to induce GnRH pulse generator activity in OVX goats (126). In the male rhesus
382 monkey, an absence of expression of SP in kisspeptin neurons has been reported but SP fibers
383 are observed in close apposition on ARC kisspeptin perikarya (127). In the ewe, only a small
384 proportion of ARC kiss neurons contain *tacr1* or SP expression. (120).

385 Recently, results in rat showed that icv injection of SP antagonizes the inhibitory effect of
386 mammalian ortholog of gonadotropin-inhibitory hormone (GnIH), RFRP-3, on the expression of
387 hypothalamic *gnrh* and *kiss1* (123). These first data suggest that SP may act at different levels of
388 the central control of HPG (GnRH, kisspeptin or GnIH). More studies in mammals and in other
389 vertebrates should be performed to see whether this effect of SP on GnIH action is conserved
390 throughout evolution.

391 **2.1.1.2.2. Teleosts**

392 In zebrafish, direct actions of TAC1 peptides are more likely on GnRH than on Kiss neurons, as
393 associations between TAC1-immunoreactive processes and neurons for GnRH3 (the
394 hypophysiotropic GnRH form in this species) in the ventral telencephalic area are observed,
395 while there is no apparent proximity of TAC1 processes to kiss2 mRNA-expressing neurons in the
396 hypothalamus (61). Recently, expression of *tacr1a* mRNA was reported in several brain regions
397 containing GnRH3, as well as Kiss2, cells such as olfactory bulb, preoptic area and hypothalamus
398 (128), leading the authors to suggest that TAC1 peptides may act on both neurons. To the best
399 of our knowledge, no functional study has been yet performed to investigate the action of TAC1
400 peptides on GnRH production in teleosts.

401 **2.1.1.3. Effects of TAC1 peptides on LH and FSH expression, synthesis and release**

402 **2.1.1.3.1. Mammals**

403 A direct action of SP and NKA at the pituitary level is possible as expression of their receptors
404 has been detected in pituitary cells, and sometimes specifically on gonadotrophs, in mammals
405 [*tacr1* (129–131); *tacr2* (132)]. Moreover, SP and NKA fibres have been reported surrounding
406 hypophyseal blood capillary vessels in the median eminence and these peptides to be present in
407 the pituitary of mammals [NKA, rat (133); SP, rat (134–137); SP, NKA, rat (138); SP, rhesus
408 monkey (127,139)]. The first reported study on the *in vitro* effect of tachykinin on gonadotropins
409 dates back to 1974. Fisher and colleagues observed that SP induced release of LH and FSH by
410 pituitaries, from intact rats, cultured *in vitro* (140). This preliminary data using few pituitaries
411 and high dose of SP was followed by a contradictory one, that reported no effect of SP on LH
412 and FSH release by hemi-pituitaries of OVX rats (141). These first data already point out the
413 potential importance of sex steroid on SP action in the control of gonadotropins. A stimulatory
414 effect of SP on LH release from anterior pituitary cells in culture is reported during peripubertal
415 period in male and female rats, but not at prepubertal age and long after maturation (142). *In*
416 *vitro* perfusion of anterior pituitaries from female rats allowed to show an inhibition of GnRH-
417 induced LH release by SP, an effect abolished by the use of TACR1 antagonist (143). All these
418 results obtained in rat highlight the sex steroid dependence of the *in vitro* effect of SP on
419 gonadotropins in this species. Data are also available in another mammal, the pig. In cultured
420 porcine gonadotrophs, SP was reported to stimulate LH release without affecting intracellular LH
421 content (144). It also potentiated GnRH-stimulated LH release and reversed GnRH-induced
422 decrease of gonadotroph LH stores, these effects not being blocked by the use of GnRH-

423 receptor antagonist. A few years later, the same group demonstrated that SP direct effect on pig
424 gonadotrophs and LH release was extracellular Ca^{2+} -dependent and did not involve effect on *lhβ*
425 transcript levels (145). Altogether, these *in vitro* data in mammals converge towards a
426 predominantly stimulatory effect of SP on LH release (Figure 2). Concerning NKA, few data are
427 available. Incubation of hemi-pituitaries with NPK and NPy stimulates LH release in intact male
428 rats, but is not significant in castrated animals, while no significant effect is seen with NKA in
429 both situations (146).

430 *In vivo* data concerning SP and NKA action on gonadotropins in mammals have been reviewed
431 by Fergani and Navarro (99) and the following text will give a summary of them, complemented
432 with one more recent publication (122). These *in vivo* studies, which cannot discriminate
433 between direct and indirect effects, report diverse effects of TAC1 peptides on LH and FSH
434 release, mostly depending on the presence or absence of sex steroids, and also likely due to
435 species-differences [for review: (99)]. Most of these studies reported a stimulatory effect of SP
436 on LH release [OVX+E2 female rat (147); prepubertal female and male rats (148); normal men
437 (149); intact female rabbit (150); OVX+E2 female mouse and intact male mouse (115);
438 prepubertal female mouse (109); intact ewe (120)]. However, an absence of effect was
439 sometimes observed [intact adult male rat (146); intact adult female rat (148); OVX female rat
440 (146,147); castrated male monkey (127); OVX or OVX+E2 female goat (126)]. And even inhibition
441 was reported in castrated male rats (146,151). Intravenous (iv) injections of SP failed to induce
442 LH release in the rhesus monkey (127). However, in the cynomolgus monkey, there is a
443 reduction in the duration and amplitude of LH surge after intragastric administrations of TACR1
444 antagonist (152). In the ewe, much higher doses of SP compared to NKB are needed to stimulate
445 LH release (120). Similarly, for NKA, various effects were obtained depending of the 'sex steroid
446 status' of the animals. Stimulation of LH release was observed in intact mature animals [male rat
447 (146); OVX+E2 female mouse and intact male mouse (115,148)] and in prepubertal intact male
448 and female rats (148), while inhibition was reported in castrated animals [male rat (146); female
449 rat (146); female mouse (115)]. An absence of effect was also sometimes seen by some authors
450 in OVX adult female rat (121). Recently, the stimulatory action of NKA in the presence of sex
451 steroids during adulthood in female mouse was reported to be NKB-independent, as NKA was
452 able to induce LH release in NKB-deficient mice (*tac3KO* mice) or after blockade of TACR3 by
453 specific antagonist (122). In addition, the stimulatory effect of NKA was kisspeptin-dependent,
454 as it was absent in *Kiss1KO* mice (122). Interestingly, the inhibitory action of NKA on LH release
455 in the absence of sex steroids during adulthood in female mouse was found to be NKB- and
456 dynorphin-dependent (122). In the ewe, much higher doses of NKA are needed to stimulate LH
457 release, compared to NKB (120). In the female goat, NKA agonist was inefficient to induce LH
458 release either in OVX or OVX+E2 animals (126). NPK was also shown to modulate gonadotropin
459 as icv injection of the peptide produced a suppression of LH release in ovariectomized rats (146).

460 A few studies addressed the effects of TAC1 peptides on FSH release in rodents. A sex difference
461 was obtained in prepubertal rats: acute administration of TACR1 agonist stimulated it only in
462 females, while it was TACR2 agonist that was able to induce it in males (148). In intact adult rats,
463 TACR1 agonist had no effect on FSH release in both sexes and TACR2 one could elevate it in
464 females (148). SP was ineffective in stimulating FSH release in OVX+E2 rats (147). In the intact
465 male mice, central injection of TACR1 or TACR2 agonists induced an elevation of FSH secretion
466 (115).

467 **2.1.1.3.2. Teleosts**

468 A direct action of tachykinins at the pituitary level is also possible in teleosts as SP fibres directly
469 innervate the pituitary (59,153,154). Moreover, TACR1 expression has been detected in the
470 pituitary [zebrafish: (72); grass carp (63,76)] and specially in LH cells [grass carp: (62)]. In
471 contrast, in grass carp pituitary, spatial distribution of TACR2 is only overlapping with prolactin
472 cells (62,155), and not LH cells (62). FSH cells were not investigated in these studies (62,155).

473 To date, only one study investigated the direct effects of peptides encoded by *tac1* gene on
474 teleost pituitary hormone expression and release [Figure 2, (62)]. Using primary culture of
475 prepubertal grass carp pituitary cells, Hu and collaborators showed that grass carp SP and NKA
476 could elevate prolactin (*prl*) and somatolactin- α (*sl α*) mRNAs and hormone secretion, without
477 any effect on proopiomelanocortin (*pomc*), *fsh β* , thyrotropin β (*tsh β*), glycoprotein α -subunit
478 (*gp- α*), growth hormone (*gh*) and *sl β* expression. For LH, SP but not NKA could induce a dose-
479 dependent inhibition of *lh β* mRNA levels (after 24h of treatment), while both peptides induced a
480 dose-dependent stimulation of LH release with a lower potency and efficacy for NKA (after 3h).
481 This induction of LH release by SP and NKA, as well as the inhibition of *lh β* mRNA by SP, were
482 blocked by the use of TACR1 antagonist, but not of TACR2 or TACR3 antagonists, in agreement
483 with the fact that TACR1 was the only form of TACRs detected in grass carp gonadotrophs.
484 Moreover, SP was able to partially suppress GnRH induction of *lh β* mRNA, while co-treatment
485 with TACR1 antagonist enhanced this induction. TAC1 peptides in grass carp can thus have
486 differential effects on LH release and *lh β* mRNA levels via activation of TACR1 in gonadotrophs.
487 More studies in other teleost species are needed to decipher whether these actions are species-
488 specific or common to all teleosts.

489 **2.1.2. TAC3 peptides**

490 **2.1.2.1. Inactivation of TAC3 system and reproduction**

491 In 2003, Pintado and collaborators injected intraperitoneally an antagonist of TACR3, the
492 preferential receptor for TAC3 peptides, to 8-week-old female rats and showed no effect on
493 reproductive success or litter size, while at 6-month-old subcutaneous injection of the same
494 antagonist resulted in a reduction in the litter size (113). Later, mutations in the *tac3* or in the
495 *tacr3* genes were characterized which lead to hypogonadotropic hypogonadism in human
496 [(156–161); for review: (162)], that could be reversed in adulthood (159). Similarly, in mice, *tac3*
497 (163) or *tacr3* (164) null females show delayed sexual maturation and abnormal estrous
498 cyclicity, which recover in adulthood leading to fertility, although they produced fewer pups per
499 liter. In contrast, timing of sexual maturation and fertility are preserved in *tac3* (163) or *tacr3*
500 (164) null males. In a teleost, the zebrafish, the knockout of either *tac3a*, *tac3b* or both does not
501 disrupt the reproduction (spermatogenesis and folliculogenesis are not impaired) (165). The
502 impact of *tac3* gene mutation should be now studied in other teleost species, as knockout
503 studies of reproductive genes such as the different types of *gnrh* [*gnrh3*: (166); *gnrh2*: (167)]
504 and *kiss* [*kiss1*, *kiss2*, *kissr1* and *kissr2*: (168)] system genes all generate zebrafish with normal
505 gametogenesis, suggesting that this species may have high compensatory mechanism [for
506 reviews: (169,170)] and may not reflect the situation observed in all teleosts.

507 **2.1.2.2. Effects of TAC3 peptides on GnRH expression, synthesis and release**

508 **2.1.2.2.1. Mammals**

509 In mammals, the first analysis of *tacr3* expression was performed in rodents and showed its
510 presence in GnRH neurons, indicating a possible direct effect of TAC3 on GnRH [rat (171); mouse

511 (172)]. However, an absence of direct regulation of GnRH release by NKB was demonstrated
512 using hypothalamic explants from adult male mice (173). In addition, in the same *in vitro*
513 system, NKB was able to completely abolish the stimulation of GnRH release induced by
514 kisspeptin (173). These results in mouse suggested that NKB could regulate GnRH only via an
515 action on kisspeptin (Figure 2), which is in agreement with the more recent demonstration of a
516 minimal expression of *tacr3* in GnRH neurons, but its expression on virtually all KNDy neurons, in
517 this species (115,174). In female sheep, no TACR3 immunoreactivity was revealed in GnRH
518 neurons, but GnRH neurons and fibres were in proximity to NK3R-containing ones (175). Use of
519 the immortalized GT1-7 cell line, which represents mature post-migratory GnRH neurons with
520 expression of TACR3, allowed to show differential effects on GnRH release depending on the
521 length of exposure: acute treatment with NKB increases GnRH secretion, while long-term
522 treatment decreases it by repressing transcription (176). In the arcuate nucleus of the
523 hypothalamus, TAC3 is co-expressed with kisspeptin and dynorphin in the so-called KNDy
524 neurons [for review: (100)]. This was first demonstrated in sheep (98). KNDy neurons project to
525 GnRH neurons and positively regulate their activity, being responsible for the generation of
526 GnRH pulsatility in the hypothalamus of mammals [for reviews: (99,177,178)]. Ablation of these
527 neurons in female rats induces hypogonadotropic hypogonadism (179). Most of the studies
528 show that neurons of ARC and particularly KNDy neurons project to the axonic terminals of
529 GnRH neurons (100). Therefore it is possible to assume that KNDy neurons might act on those
530 terminals in a direct manner or using intermediate neurons to regulate the GnRH release (177).
531 The most accepted hypothesis for mammalian KNDy neurons proposes that TAC3 acts in a
532 positive manner and that Dyn acts in a negative way on the pulsatile release of kisspeptin by
533 KNDy neurons (174,180). In the ewe also, a high percentage of kisspeptin neurons produces
534 dynorphin and NKB (98). A recent review addresses the question whether the KNDy model for
535 the control of GnRH pulses apply to humans and other primates, compiling data showing that
536 colocalization of kisspeptin and NKB is also observed in rhesus monkeys and humans (181). In
537 addition, the ability of kisspeptin to induce LH release in patients with mutations in TAC or
538 TACR3 tends also towards a proximal action of NKB to kisspeptin in stimulating GnRH secretion
539 (182).

540 *In vivo* studies in different mammals have shown the stimulatory effect of NKB on GnRH
541 secretion [prepubertal and pubertal rhesus monkeys: female (183) and male (184); ewe (185);
542 goat (126,170). Electrophysiological studies showed that icv administration of TACR3 agonist
543 (senktide) suppressed GnRH pulse generator in OVX rats (186), while it induced GnRH release in
544 intact male mice (187).

545 **2.1.2.2.2. Teleosts**

546 In tilapia, Mizrahi and colleagues investigated the coexpression of the 3 different forms of GnRH
547 present in this species with TACR3s. They show that GnRH3 neurons expressed *tacr3a*, but not
548 *tacr3b*, while the contrary was observed for GnRH2 neurons, and GnRH1 ones expressed both
549 *tacr3* (188). In the striped bass, TAC3 peptides, NKB and NKBRP (NKF in the article) have an
550 inconsistent effect (no or stimulatory only at highest dose) on *gnrh1* expression by brain slices in
551 culture, while persistently downregulating *kiss2* expression (75) (Figure 2).

552 In contrast to human and rodents, the expression of tachykinins and kisspeptins are not always
553 expressed in the same neurons in teleosts. In the zebrafish, NKB/TAC3 and NKF/NKBRP/TAC3RP
554 are expressed in the *nuclear lateralis tuberis* (NLT), which is the teleost homologous structure to
555 the ARC (189), but *kiss2* expression has not been found in this area (190). This finding in

556 zebrafish, however, does not exclude that TAC neurons project on kisspeptin ones. In the striped
557 bass, NKB neurons innervate the largest kiss2 neuronal population in the hypothalamus, which
558 also expresses TACR3, while no expression of TACR3 or no NKB neuronal projections is detected
559 for GnRH1 soma (75). In addition, in this species, TAC3 peptides, NKB and NKBRP (NKF in the
560 article), are able to down-regulate *kiss2* gene expression *in vivo*, while having no effect on *gnrh1*
561 expression (75). In addition, cotreatment with a NK3R antagonist abolishes the negative effect
562 of TAC3 peptides on *kiss2* mRNA levels (75). These results in the striped bass suggest that
563 tachykinin peptides may act preferentially on the kisspeptin system, as in mammals. When
564 injected to goldfish females in mid-vitellogenesis and males in late-spermatogenesis, three NKB
565 peptides (NKBa-13, NKBa-11 and NKBb-13), but not the fourth one (NKBb-11), increase
566 hypothalamic *gnrh3* mRNA levels (191). NKBa-10 and NKBa-13 ip injected to goldfish females at
567 early vitellogenic oocyte stage and males at early spermatogenesis stage decrease mRNA levels
568 of both hypothalamic *kiss2* and *gnrh3* (except NKBa-13 on *gnrh3*) (90). In tilapia, NKBRP injected
569 to mature male tilapia inhibits the expression of brain *gnrh-1* and *kiss2*, while NKB has no effect
570 (192). A recent study in the Japanese eel, *Anguilla japonica*, reports that ip injection of each of
571 the four mature peptides found in this species gives different effects depending on the peptides
572 and the doses used: low dose of the four peptides had no effect on neither *gnrh1* (*mgnrh*) and
573 *gnrh2* (*cgnrh*) expression, while high dose of NKBa-10 and NKBb-13 (and not NKBa-13 and NKBb-
574 10) stimulates *gnrh1* expression (193). All these data demonstrate that different regulations of
575 *gnrh* and *kiss* expression by TAC3 peptides (from none to stimulatory or inhibitory effects) may
576 be encountered among teleosts, depending on the species, the maturity stage, the doses and
577 the peptides tested.

578 The non-systematic action of TAC3 peptides on GnRH and kisspeptin in teleosts, compared to
579 the situation observed in mammals, is likely due to the surprisingly non-essential character of
580 these two neuropeptides for reproduction in some teleost species. Indeed, recent knockout
581 studies demonstrated that *gnrh3* and *gnrh2* in zebrafish (166,194), *gnrh1* in male medaka (195),
582 as well as *kiss1* and *kiss2* in zebrafish (168) and medaka (196) were dispensable for normal
583 reproductive function. In zebrafish, even triple mutants for *gnrh3*, *kiss1* and *kiss2* undergo
584 normal puberty and gonad maturation (197). These lack of effect on reproduction of GnRH and
585 kisspeptin gene editing led many scientists to make assumptions on the possibility of
586 physiological compensatory phenomenon in teleosts (for reviews: 169,198–200). Besides these
587 knockout results, many data are available, stating reproductive actions of GnRH (for review:
588 199) and kisspeptins at various HPG levels in teleosts (for reviews: 200,201).

589 **2.1.2.3. Effects of TAC3 peptides on LH and FSH expression, synthesis and release**

590 **2.1.2.3.1. Mammals**

591 A direct action of tachykinins at the pituitary level is possible as *tacr3* expression has been
592 detected in this gland in mammals [ewes (202); pigs (203) and gilts (204)]. Moreover, NKB fibres
593 have been reported surrounding hypophyseal blood capillary vessels in the median eminence
594 [monkeys (205)]. To the best of our knowledge, only one *in vitro* study has investigated the
595 potential direct effect of NKB on gonadotropins in mammals, by using a gonadotroph cell line
596 (206). The authors reported no effect of NKB on *lhβ* and *fshβ* mRNA expression, even if TACR3
597 was detected in this cell line.

598 Comparing various tachykinins *in vivo*, Sahu and Kalra (121) were the first to report that NKB-
599 containing implants, in the third ventricle of OVX rat brain, did not induce any change in LH

600 release. Later, this absence of NKB effect on LH was also shown after either ip or icv
601 administration to intact adult male mice (173). However, evidence for stimulatory effects of NKB
602 on LH has since been documented in many mammalian species [for reviews: (99,181,207)], as
603 for example in prepubertal female rats (16,208). In some studies, the stimulatory effect of NKB
604 on LH is only observed under physiological sex steroid levels (i.e. intact or OVX+E2 adult animals)
605 [adult male and female mice (115,209); adult male and female rats: (209,210); lactating female
606 cattle: (211)]. In contrast, in monkeys, NKB is able to stimulate LH release in castrated juvenile
607 (205,212) and adult (213) males. In the sheep, castration does not prevent the stimulatory
608 action of NKB in adult females (213,214), as compared to intact females [adult: (108,215);
609 prepubertal: (216)]. Similar situation is observed in the female goat with stimulatory effect of iv
610 administered NKB agonist (senktide) (126) or no effect of icv injected NKB (180), regardless of
611 the gonadal status. Recently, iv administration of senktide has even been shown to be efficient
612 in stimulating LH release in fetal male and female sheep (217). In humans, early studies report
613 no gonadotropin-stimulating effect of NKB iv administered in adult men and women (218,219),
614 but a series of data obtained by Skorupskaite and collaborators using TACR3 antagonist given
615 orally show a decrease of overall circulating LH levels and LH pulsatility in adult men (220) and
616 women (221–223). Few studies report an inhibitory action of senktide on LH release, regardless
617 of the steroid milieu in female rat (186,224), or only in the absence of sex steroids in female
618 mouse (174).

619 Concerning FSH, either stimulatory [mouse: (115,148,225); monkey: (213); man: (220,226)] or
620 no effect [mouse: (173); rat: (148); woman: (218,220,226); man: (218,219)] of NKB has been
621 reported.

622 These various effects on LH and FSH in mammals could be due to species, physiological status,
623 or mode of peptide administration. Table 1 gives details on all these *in vivo* studies of NKB action
624 on gonadotropins.

625 **2.1.2.3.2. Teleosts**

626 TACR3s (*tac3ra1*, *tac3ra2* and/or *tac3rb*) are expressed at the pituitary level in various teleosts
627 [zebrafish: (26,72); spotted sea bass: (79); grass carp: (63,91,227,228)] and in both LH and FSH
628 cells in tilapia (73), making a direct effect of NKB and NKBRP possible on gonadotropin synthesis
629 and release. Interestingly, in the grass carp, Xu and collaborators reported that *tacr3a* is
630 expressed in both LH and somatolactin α (SL α) cells, while *tacr3b* expression is only found in SL α
631 cells (91). FSH cells were not investigated in this study (91). In tilapia, when NKB and NKBRP are
632 applied to mature male pituitary cells, they both increase FSH and LH release (73). In culture of
633 pituitaries from mixed sexed juveniles of this species, NKBRP downregulates *fsh β* and *lh β*
634 mRNAs, while NKB has no effect (192). Still in tilapia, Mun and colleagues recently compared
635 responses of pituitary cells and pituitaries to NKB and NKF in males and females. They reported
636 that expression of *fsh β* and *lh β* mRNAs did not show any change after treatment of whole
637 pituitaries with NKB or NKF in both sexes (229). In contrast, the use of primary culture of
638 pituitary cells allowed them to find that NKB could stimulate *fsh β* and *lh β* mRNAs in female, and
639 inhibit them in male, while the contrary was observed with NKF (229). These results highlight
640 major differences according to the maturation stage, to the protein or mRNA, or to the type of
641 culture (primary cell culture versus organotypic culture) concerning the effects TAC3 peptides
642 on gonadotropin in tilapia. The other studies available suggest in addition species-differences,
643 using the same method, primary cultures of pituitary cells (Figure 2). In the striped bass, the

644 effects of NKB and NKBRP were stimulatory on LH and FSH release, but absent on their mRNAs
645 (75). In the European eel, the four peptides encoded by *tac3* gene were able to inhibit *lhβ*
646 mRNAs by pituitary cells in culture, but had no effect on *fshβ* mRNAs (77). Some other studies,
647 using this cell culture system, reported no effect of NKB and NKBRP on *fshβ* and *lhβ* mRNAs
648 [grass carp (76); orange-spotted grouper (78)].

649 In teleosts, most of the *in vivo* data showed increase of gonadotropin release and expression
650 after treatment with TAC3 peptides. In zebrafish, homologous (zebrafish) NKBa and NKBRP (NKF
651 in the article) induce LH release when injected to mature females (72). Among the four
652 neurokinin B peptides characterized in zebrafish, the NKBb presents a modified C-terminal motif
653 from the typical tachykinin FVGLM to FVGLL thus losing the final methionine. This change leads
654 to decreased affinity of this peptide for the two TACR3 and highly reduced *in vivo* effect,
655 compared to other neurokinin peptides (72,74). However, the finding of a third TACR3 in the
656 zebrafish genome (26) increases the chances that the NKBb with different C-terminal motif may
657 be active. In tilapia, ip injections of homologous NKB to mature males increase both FSH and LH
658 plasma levels, while homologous NKBRP induces only LH release (73). In mature female tilapia,
659 ip injection of tilapia NKB and NKBRP has no effect on pituitary *lhβ* and *fshβ* mRNA levels (188).
660 More recently, Mizrahi and colleagues developed specific NKB and NKBRP (NKF in the article)
661 analogs based on the structure of the mammalian NKB analog, senktide (188). When ip injected
662 to mature female tilapia, these analogs increase plasma LH levels as native (tilapia) NKB and
663 NKBRP do, and they are even able to increase FSH release while native ones have no effect
664 (188). Concerning mRNA levels, native NKB and NKB analog are efficient in stimulating *lhβ* and
665 *fshβ*, whereas native NKBRP has no effect and NKBRP (NKF in the article) analog stimulates only
666 *lhβ* (188). When injected to goldfish females at mid-vitellogenesis and males at late
667 spermatogenesis, homologous NKBa-10, NKBa-13 and NKBb-10, but not NKBb-11, increase
668 pituitary *lhβ* mRNA levels (191). Increase of *fshβ* mRNA levels is observed in females only after
669 administration of goldfish NKBa-13 and NKBb-13, while in males all peptides, except NKBb-11,
670 induce these levels (191). In sexually immature goldfish, NKBa-10 and NKBa-13 ip injected to
671 females at early vitellogenic oocyte stage and males at early spermatogenesis stage decrease
672 mRNA levels of both pituitary *lhβ* and *fshβ* (90). In the female orange-spotted grouper
673 *Epinephelus coioides* at early vitellogenic stages, ip injection of NKB increases pituitary *lhβ*, but
674 not *fshβ*, mRNA levels, while administration of NKBRP has no effect on these expressions (78). A
675 recent study in the Japanese eel reports that ip injection of each of the four mature peptides
676 found in this species gives different effects depending on the peptides and the doses used: high
677 dose of the four peptides inhibits *lhβ* and *fshβ* expression, while low dose of NKBa-10 and NKBb-
678 13 stimulates them (193). All these data show various effects of TAC3 peptides on gonadotropin
679 release and expression among teleosts, depending on the species, the maturity stage, the doses
680 and the peptides tested. Table 1 compiles all these *in vivo* studies of NKB action on
681 gonadotropins.

682 **2.1.3. TAC4 peptides**

683 Little is known on the effects of TAC4 peptides, HK and EK, on central reproductive brain-
684 pituitary axis. To the best of our knowledge, the only available study was realised in a teleost,
685 the grass carp. Using transcriptomic analysis of TAC4 peptide effects on pituitary cells, Shi and
686 colleagues recently demonstrate that HK2 downregulates the pituitary expression of one GnIH
687 receptor (GnIHR3), five estrogen receptors (nuclear: ESR1, ESR2a, ESR2b and ESRRβ; membrane:
688 GPER1), while upregulating the expression of another nuclear estrogen receptor (ESRRγ) (63)

689 (Figure 2). In mammals, the known reproductive role of HK1 takes place at the peripheral level
690 (33), while up to now, none is attributed to EKs.

691 **2.2. At the peripheral level**

692 Tachykinins can also act at the levels of the gonads and the secondary sex organs, via paracrine
693 and autocrine effects, in both females and males (Figure 2).
694

695 **2.2.1. Effects on female reproductive system**

696 **2.2.1.1. Mammals**

697 A review has already been dedicated to tachykinin involvement in mammalian ovarian function
698 (230), and the text below is only a summary. Expression of *tac1* and *tac3* (mRNA), as well as
699 their receptors, is detected in the mammalian ovary, oocytes and granulosa cells (113,230),
700 indicating potential autocrine/paracrine effects. Isolated cumulus granulosa cells in mouse
701 express *tac1*, *tac3* and *tac4* (113). The control of ovarian steroid secretion by tachykinins in
702 mammals has been previously reviewed (230). Briefly, data were obtained in various
703 mammalian species with different results. In rat, exposure of granulosa cell culture or ovarian
704 fragment in culture with SP and SP analog was unable to modify estrogen or progesterone
705 release (231). In hamster, depending on the age of the animals, treatment of ovaries in culture
706 with SP could stimulate (15-day old hamsters) or inhibit (adult hamsters) or have no effect
707 (neonatal hamsters) on estradiol release (232). Concerning progesterone release, in the same
708 culture system, SP has a stimulatory effect (neonatal and adult hamsters), or no (15-day old
709 hamsters) effects (232). Using luteal cells in culture and exposure to SP, opposite results were
710 obtained on progesterone release in basal conditions or under stimulation with LH in two
711 different artiodactyla/ungulata species: stimulation in bovine (233) and inhibition in pig (234). In
712 pig, SP treatment did not change estradiol release by granulosa cells in culture, but stimulated it
713 by luteal cells (234). These various effects of SP on *in vitro* ovarian sex steroid release in
714 mammals thus likely depend on species, type of cells and age of animal.

715 Genes encoding tachykinin peptides (*tac1*, *tac3* and *tac4*) and receptors (*tacr1*, *tacr2* and *tacr3*)
716 are all expressed in the uterus of mouse (46,113,235), rat (236) and human (237,238),
717 suggesting potential autocrine/paracrine effects. Their expression change during the estrous
718 cycle and during pregnancy [mouse: (46); rat: (239,240)]. TACR2 is involved in human uterine
719 contraction and is regulated during pregnancy (33). An altered expression of SP, NKA, HK1 and
720 their receptors is observed in uterine leiomyomata in human (241). When applied to isolated
721 myometrium from non-pregnant women, SP, NKA and NKB, produce contractions, while TACR2
722 receptor-selective antagonist abolishes the uterotonic effect of NKA agonist (237). These TAC
723 peptides also produce a direct contractile effect on uterine smooth muscle in mouse (5,242), rat
724 (235,240,243), and pregnant woman (237,244). Human HK1 is also a uterine stimulant in the
725 human (33).

726 In the rat placenta, downregulation of *tac3* and *tacr3* expression is associated with pregnancy
727 (41). NKB placental levels are increased at term labor in women (245). In the placenta of pre-
728 eclampsia women, elevated circulating NKB, as well as increased *tac3* expression, are reported
729 as compared to placenta of normal pregnant women (41,71,246). TAC3 and TACR3 may
730 contribute to pre-eclampsia during late pregnancy (41,247). NKB stimulates the expression of
731 *gnrh*, *kiss* and human chorionic gonadotropin (hCG) by primary cultures of rat placental cells
732 (248).

733

2.2.2.1.2. Teleosts

734 An autocrine/paracrine action is also possible in teleosts as both NKB and NK3R are expressed in
735 the ovary [zebrafish: (26,72); tilapia: (73)]. In the zebrafish, a direct effect of neurokinin B on the
736 ovary is reported, as it stimulates estradiol production and increases the expression of *cyp11a1*
737 and *cyp19a1* in primary cultures of follicular cells (249).

738

2.2.2. Effects on male reproductive system

739

2.2.2.1. Mammals

740 The involvement of tachykinins in the regulation of mammalian testicular function has already
741 been reviewed (242,250,251), and the text below is a brief summary.

742 SP inhibits testosterone production and release by isolated Leydig cells in hamster (252,253).
743 *Tac1*, *tac3* and *tac4* genes are expressed in the human sperm (254). Tachykinins are likely to
744 enhance the sperm motility by TACR1 and TACR2 dependent mechanisms, as TACR1- and
745 TACR2- (but not TACR3-) selective antagonists can reduce the stimulating effect of
746 phosphoramidon in human (254). Human HK1 also promotes progressive sperm motility (Figure
747 2) with a potency similar than that of NKA, (lower than that of SP and higher than that of NKB)
748 (255). All classical TACRs seem to be involved in these actions, but the role of TACR1 was
749 predominant (255).

750 Tachykinins also stimulate contractility of the *vas deferens* and of seminal vesicles [Figure 2, for
751 review: (242)]. SP (TAC1RP) and NKA (TAC1) are present in the prostate of guinea pig and rat at
752 low levels, of dog abundantly and absent in human prostate [for review: (242)], while *tac1*, *tac3*
753 and *tac4* mRNA expressions have been detected in human prostate (39,238). Prostate
754 contraction by tachykinins in human involves TACR2 (256).

755

2.2.2.2. Teleosts

756 An autocrine/paracrine action is also possible in teleosts as both NKB and NK3R are expressed in
757 the testis [zebrafish: (72); tilapia: (73)]. In tilapia, recent use of NKB antagonists by ip injections
758 on adult males reduced the number of spermatozoa, leading to lower fertility (257), an effect
759 which can be direct as male tilapia have significant amounts of TACR3 in the testis (73).
760

761 3. Physiological role of tachykinins in the regulation of food intake

762 As described previously in this review, TAC peptides (SP and NKA) were discovered for their
763 contractile role on gastrointestinal tract (GIT) in mammals. However, far less direct evidences
764 are available concerning the regulation of food intake by tachykinin peptides when compared to
765 their role in reproduction. Nevertheless, recent data, notably in two teleosts, the sea bass
766 *Dicentrarchus labrax* and the grass carp, highlight a potential major regulatory role of TAC3 and
767 TAC4 peptides in the regulation of genes involved in feeding and gut motility.

768 The control of food intake involves two major populations of ARC hypothalamic neurons, in
769 mammals as well as in other vertebrates: neurons producing neuropeptide Y (NPY) and agouti-
770 related peptide (AgRP), which are orexigenic (appetite stimulator) peptides, and neurons
771 producing proopiomelanocortin (POMC) and cocaine-and-amphetamine regulated transcript

772 (CART), which are anorexigenic (appetite inhibitor) peptides [Figure 3; for reviews: (12,258–
773 262)]. These hypothalamic neurons integrate information from peripheral hormones such as
774 leptin, an anorexigenic hormone produced by adipose tissue in mammals and by liver in
775 teleosts, and ghrelin, an orexigenic stomachal hormone [Figure 3; for reviews: (12,258–262)].

776 As gut peptides, tachykinins have also potential direct role on the GIT in vertebrates. A well-
777 described one is the stimulation of its motility, the first necessary step of food digestion after its
778 intake [for review: (263)].

779 **3.1. Mammals**

780 **3.1.1. Energy state and tachykinin system**

781 TAC3-neurons, mainly as part of KNDy neurons, have been involved in the regulation of both
782 negative and positive energy balance. For example, they mediate the anorexigenic effect of
783 estradiol in young female rats, as selective ablation of KNDy neurons suppresses the post-
784 ovariectomy weight gain (264). In addition, many studies report regulation of tachykinin system
785 by a change of energy status. Fasting and caloric restriction (CR) induce a decrease in
786 hypothalamic ARC *tac3* and/or *tacr3* expression in rodents [pubertal female rat (265); OVX
787 female mice (266); adult female rat (267)]. Nevertheless, in adult male mice, fast increase
788 hypothalamic ARC *tac3* and *tacr3* (173), while CR and fast (267,268) have no effect in adult
789 female rats. In sheep, chronic food restriction down-regulates *kiss* and *tac3* mRNA levels
790 [castrated male sheep: (269); OVX ewe lambs: (270); for review: (271)]. Feeding high-fat diet
791 does not change ARC mRNA levels for *tac3* in pubertal female mice (272) while it has a
792 stimulatory effect in pubertal female rat (273). All these data suggest differential regulation of
793 tachykinin system (and of its involvement in the control of metabolism) according to species,
794 sexual maturation stage, and/or degree of negative energy balance.

795 **3.1.2. Effects of tachykinins on food intake and GIT motility**

796 Abundant distribution of TAC1, TAC2 and TAC3 receptors is found in the hypothalamic nuclei
797 involved in the control of food intake such as ARC, paraventricular nucleus (PVN) and lateral
798 hypothalamus (LHA) [for reviews: (4,99,207)]. Full tachykinin system is also detected in the
799 neurons and nerve fibers of the mammalian gut with remarkable diversity between species [for
800 reviews: (274–276)]. These distributions point out towards a potential involvement of TAC
801 peptides in the control of feeding and GIT motility.

802 Administration of NPK to food-deprived rats for 24h delays the onset of (re)feeding and
803 decreases the cumulative food intake [(277); for review: (278)]. Achapu and co-workers show
804 that the inhibition of food intake induced by centrally injected NPK may be due to the intense
805 grooming induced by the injection (279). Similarly, icv injection of SP to food-deprived male rats
806 suppresses food intake, but an increase of locomotor activity is also observed (280). The fact
807 that icv injections of NKA induce an increase of *pomc* mRNA levels in the rat ARC (281) also
808 argues towards such anorexigenic action of tachykinins in mammals or at least in rodents.
809 However, later, Karagiannides and collaborators consider SP as a novel anti-obesity target after
810 showing that the blockade of SP signaling by mean of an TACR1 antagonist leads to a decrease
811 of food intake and body weight in two obese mouse models, a HFD-induced one and a leptin
812 deficient (*ob/ob*) one, (282). They also report that peripheral injection of SP increases food
813 intake and induces upregulation of hypothalamic *npy* as well as downregulation of *pomc*, mRNA
814 levels (282). In male rats, ghrelin negatively regulates *tac1* gene in the hypothalamus and acute

815 icv injection of NPK and NP γ (but not SP nor NKA) reduces food intake (283). In addition, in male
816 mice, the hyperphagic effect of peripheral injection of ghrelin disappears in *tac1*KO animals,
817 suggesting the *tac1* requirement in the control of food intake by ghrelin in rodents (283). The
818 first study using *tac1* null mice does not show any difference in body size compared to controls
819 (282), while a more recent one reports that these animals have significantly lower body weight
820 during adulthood and also show increased hypothalamic *pomc* expression and reduced food
821 intake (284). All these data indicate that, in rodents, TAC1 peptides may function as either
822 endogenous anorexigenic or orexigenic peptides.

823 The capacity of SP, NKA and NKB to induce intestine contraction was one of the actions that led
824 to their discoveries (refer to part 1.1. of this review). Their action on motility is observed in all
825 parts of the gut through the tachykinin receptors and has been previously reviewed (285,286).

826 **3.2. Teleosts**

827 **3.2.1. Energy state and tachykinin system**

828 In goldfish, short-term postprandial increase in *tac1* mRNA levels (γ -PPT in the article) has been
829 reported in both the hypothalamus and the olfactory bulbs (287). In zebrafish, fasting increases
830 the brain expression of *tac3* in females (288). In grass carp, food intake can significantly induce
831 hypothalamic *tac3a* and *tac3b* mRNA expression (228). Thus, in teleosts, change in energy state
832 may have positive and negative effects on TAC system.

833 **3.2.2. Effects of tachykinins on food intake and GIT motility**

834 Immunohistochemical studies report high concentrations of tachykinins and their receptors in
835 teleost hypothalamic areas involved in the control of food intake [SP in goldfish (289); SP in sea
836 bass (153); carassin in goldfish (290); TACR1 and TACR3 in electric fish *Apteronotus*
837 *leptorhynchus* (291)]. In goldfish, the *tac1* mRNA (γ -PPT in the article) encoding SP, carassin, and
838 NKA presents higher expression in olfactory bulbs and hypothalamus, while being present
839 throughout the brain (59,287). More recently, RT-PCR, qPCR and ISH data confirmed the
840 expression in the hypothalamus of the different *tac* and *tacr* genes [zebrafish (26,72); tilapia
841 (73); grass carp (76, 62, 63, 91); goldfish (74, 90); orange-spotted grouper (78); spotted sea bass
842 (79); tongue sole (80)].

843 While tachykinins and their receptors are expressed in the teleost hypothalamus and its nuclei
844 involved in the control of food intake, to our knowledge, no data have yet shown their direct
845 effect on the expression of neuropeptides such as *pomc*, *npv* or *agrp* at the brain level. Due to
846 the direct innervation of pituitary cells by hypophysiotropic neurons in teleosts, Hu and
847 colleagues demonstrated high expression, in the brain and pituitary, of neuropeptides involved
848 in the regulation of feeding (227). They subsequently reported that TAC3 and TAC4 peptides
849 could change the expression of some of these genes, using transcriptomic analysis of TAC
850 peptide effects on grass carp pituitary cells (63,228). NKB can induce *in vitro* the expression of
851 urotensin 1 (UTS1), cocaine and amphetamine-regulated transcript 2 precursor (CART2),
852 proopiomelanocortin b (*pomcb*) and neuromedin B1 (NMB1) mRNA levels, all four anorexigenic
853 peptides, an effect that is also reported *in vivo* after ip injection (228). HK2, a peptide encoded
854 by *tac4* gene in grass carp, upregulates CART2, CART3 and CART5, peptide YY2 (PYY2), UTS1 and
855 NMB1 expression, while downregulating type 2 neuropeptide Y receptor (NPY2R) expression
856 (63). Thus, NKB and HK2 inhibit the expression of orexigenic pathway (such as NPY one) and
857 stimulate anorexigenic peptides, playing roles of satiety factors (Figure 3). In grass carp, TACR3b

858 mediates this role, while TACR3a modulates NKB action on reproduction (228), indicating a
859 typical case of subfunctionalization where paralogs share initial pleiotropic functions.
860 Tachykinins have also been involved in live prey food preference in hybrid *Siniperca chuatsi* x
861 *Siniperca scherzeri* mandarin fish as *tac 1* expression is higher in feeders compared to non-
862 feeders in this species (292).

863 Tachykinins and their receptors are also expressed in the stomach and intestine of many
864 teleosts, suggesting potential autocrine or paracrine actions [zebrafish (72, 26); tilapia (73);
865 goldfish (74, 90); grass carp (62, 155, 217); orange-spotted grouper (78); spotted sea bass (79);
866 tongue sole: (80)].

867 Peripheral action with direct contraction of the smooth gut muscle has also been described in
868 teleosts [for reviews: (10,293)]. Substance P stimulates the motility of isolated intestine or
869 stomach in a variety of fish [*Pleuronectes platessa*, *Labrus bergylta*, *Gadus* species, *Lophius*
870 species, *Anguilla* species: (56); rainbow trout: (294,295); cod *Gadus morhua*: (296,297); common
871 carp *Cyprinus carpio*: (298); bichir *Polypterus senegalensis*: (299)]. In many of these species, it is
872 demonstrated that the effect of SP is in part direct (cotreatment with tetrodotoxin, a sodium
873 channel blocker) and in part via stimulation of cholinergic and serotonergic neurons
874 (cotreatment with cholinergic or serotonergic antagonists, atropine and methysergide) [Figure
875 3, common carp: (300); rainbow trout: (294,295,299)]. NKA is also able to stimulate the motility
876 of isolated trout intestinal muscle and the vascularly perfused trout stomach, but with less
877 efficiency than SP (295). This stimulatory control of gut motility by tachykinin system takes place
878 at an early stage in development as NKA modulates zebrafish larval gut before or around the
879 time for the onset of feeding (301). More recently, an increase of the expression of *tac1* has
880 been detected by RNAseq in the giant grouper *Epinephelus lanceolatus* at the onset of feeding
881 (302). Using *in vitro* stomach and intestine incubation assays in the sea bass, Zhang and
882 collaborators showed that NKB peptides may modulate the expression of hormones (79) (Figure
883 3), known to have stimulatory activity on GIT motility in vertebrates, such as motilin and ghrelin
884 [for review: (303)]. In the stomach, NKBa-13 and NKBB-13 stimulate gastrin mRNA levels, while
885 NKB-10 peptides have no effect (79). NKBB-13 can stimulate stomachal motilin and ghrelin
886 expression, while the other three NKB peptides have no effect (79). In the intestine, NKBa-13,
887 NKBa-10 and NKBB-13 stimulate cholecystokinin mRNA levels, while NKBB-10 has no effect (79).
888 Only NKBB-10 can stimulate intestinal gastrin expression and NKBa-10 motilin expression. None
889 of the four NKB peptides can change ghrelin mRNA levels in the intestine (79).

890

891 **Conclusions and perspectives**

892 Cumulating evidence place the tachykinin system, with not only NKB (TAC3), but also other
893 tachykinin peptides, SP (TAC1) and NKA (TAC1), as major stimulatory actor in the control of
894 reproductive function, in mammals. In teleosts, the two TAC3 peptides, (NKB and NKBRP) and
895 their 3R-duplicates, can have various effects (stimulatory, inhibitory or none) mainly according
896 to the species, the maturity stage and the peptide tested. These sometimes opposite effects of
897 TAC3 peptides on reproductive genes among teleost species are also reported for other
898 neuropeptides involved in the control of HPG axis, such as kisspeptin and gonadotropin-
899 inhibitory factor (GnIH) (for review: 9). One may take into consideration the variety of
900 reproductive strategies and life cycles among these more than 25,000 different species to try to
901 find explanations, as well as the physiological compensations between neuropeptides that are
902 likely to exist in teleosts, perhaps due to the anatomical direct innervation of pituitary cells and

903 the existence of various 3R paralogs. Concerning potential involvement of TAC1 and TAC4
904 peptides in teleost reproduction, too few data are available to draw any conclusion. Past studies
905 in mammals and recent ones in teleosts suggest that the tachykinin system may also be involved
906 in the regulation of food intake and metabolism. Even if more studies are still needed, especially
907 concerning the role of TAC4 peptides, it looks like the control of food intake may be taken over
908 by TAC1 peptides in mammals, but also by TAC3 and 4 peptides in teleosts. Tachykinins and their
909 receptors thus seem to be part of networks linking metabolism and reproduction and involving
910 central and peripheral hormones, such as kisspeptin, leptin and ghrelin.

911 Due to the multiple whole genome duplication events that occurred in vertebrates,
912 phenomena of divergence and subfunctionalisation or neofunctionalisation of the ancestral
913 functions are expected and observed, especially in teleosts. Therefore, an analysis of the
914 tachykinin system is recommended for each organism of interest in order to obtain a clear view
915 of the function of this family of peptides and receptors according to vertebrate species.

916 Future studies should aim at stating whether or not KNDy neurons exist in some teleost species.
917 Too few species have been considered so far. Surprisingly, up to now, no study has yet
918 investigated the possible direct effects of TAC3 peptides on pituitary LH and FSH cells in
919 mammals; this should be performed in the future using primary cultures of pituitary cells from
920 different mammalian species. It would also be interested to study whether TAC peptides could
921 directly modify the expression of central actors involved in the control of food intake, such as
922 *pomc* and *npv*, in both mammals and teleosts. Future directions on the study of tachykinin
923 system should also include investigations on Mas-related GPCRs (Mrgprs), as TACR1 antagonists
924 have off-target activity on them (304) and substance P recruits these receptors in immune cells
925 to release cytokine contributing to inflammatory pain in mice (305,306). For example,
926 characterizing Mrgprs in teleosts and knowing whether they are present in the HPG tissues will
927 help to decipher their potential involvement in the reproductive role of the tachykinin system.

928

929 **Figure legends**

930 **Figure 1. Comparison of tachykinin system in a mammal, the human and in a teleost, the grass**
931 **carp.**

932 In human (A), tachykinin system comprises 3 *tac* genes (*tac1*, *tac2* and *tac3*) encoding up to 10
933 different TAC peptides (SP, NKA, NPK and NP γ for *tac1* gene; HK1, EKA, EKB, EKC and ECK for
934 *tac4* gene; NKB for *tac3* gene) due to the existence of various spliced variants (α , β , γ and δ for
935 *tac1* and *tac4* genes; α , β and γ for *tac3* gene). These human TAC peptides bind to 3 TACR
936 (TACR1, TACR2 and TACR3) with different affinities: SP, HK1, EKA and EKB for TACR1; NKA, NPK,
937 NP γ for TACR2; NKB for TACR3.

938 In teleosts (B), due to the teleost-specific whole genome duplication (3R), duplicates for *tac1*
939 (*tac1a* and *tac1b*), *tac3* (*tac3a* and *tac3b*) and *tac4* (*tac4a* and *tac4b*) exist and up to 12 different
940 TAC peptides have been identified up to now. Up to 6 TACR have been yet characterized: 2
941 TACR1 (TACR1a and TACR1b), one TACR2 and 3 TACR3 (TACR3a1, TACR3a2 and TACR3b). One of
942 the 3R-duplicated *tacr2* paralog (*tacr2b*) was lost in the teleost lineage but conserved in the eels
943 (elopomorphs) (Campo et al. in preparation). Binding studies with the complete available
944 tachykinin system have only been performed in the grass carp, the unique teleost species for
945 now in which *tac4* gene has been identified and published. In this species, *tac4b* and *tacr2b*

946 have not yet been identified and appear in transparency in the figure. For more information,
947 please refer to part 1 of this review. EKA, endokinin A; EKB, endokinin B; EKC, endokinin C; EKD,
948 endokinin D; HK1, hemokinin 1; HK2, hemokinin 2; NKA, neurokinin A; NKB, neurokinin B;
949 NKBRP, neurokinin B-related peptide; NPK, neuropeptide K; NP γ , neuropeptide gamma; SP,
950 substance P; TAC, tachykinin peptide; *tac*, tachykinin gene; TACR, tachykinin receptor (protein);
951 *tacr*, tachykinin receptor gene.

952 **Figure 2. Direct effects of TAC peptides in the control of reproductive function in mammals**
953 **and teleosts.**

954 TAC peptides can act directly at all the levels of the HPG axis (hypothalamus, pituitary, gonads in
955 both mammals (A) and teleosts (B), and other peripheral reproductive organs in mammals). At
956 the brain level (hypothalamus), the effect of TAC on GnRH is likely kisspeptin-dependent in both
957 mammals (KNDy neurons) and teleosts. At the pituitary level, while TAC action is only
958 stimulatory on gonadotropins in mammals, a species-specificity is observed in teleosts with
959 either no, stimulatory or inhibitory effects. At the peripheral level, TAC can act on ovarian
960 steroidogenesis in mammals (either no, positive or negative effects) and teleosts (positive
961 effects). In mammals, a positive effect is also noted on the contraction of secondary sex organs
962 (uterus in female; vas deferens, seminal vesicles and prostate gland in male), as well as on
963 sperm motility in male. For more details and for data from *in vivo* experiments, please refer to
964 part 2 of this review and to Table 1. +, direct stimulatory effect; -, direct inhibitory effect; 0, no
965 direct effect; *cyp11a1*, gene encoding cholesterol side-chain cleavage enzyme P450_{scc}; *cyp19a1*,
966 gene encoding aromatase; Dyn, dynorphin; E2, estradiol; ESR, nuclear estrogen receptor; FSH,
967 follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; GnIH-R, gonadotropin-
968 inhibitory hormone receptor; GPER, G-protein coupled (membrane) estrogen receptor; hCG,
969 human chorionic gonadotropin; HK1, hemokinin 1; HK2, hemokinin 2; kiss, kisspeptin; LH,
970 luteinizing hormone; NKA, neurokinin A; NKB, neurokinin B; NPK, neuropeptide K; NP γ ,
971 neuropeptide gamma; P, progesterone; SP, substance P; T, testosterone.

972 **Figure 3. Direct effects of TAC peptides in the control of food intake and gut motility in**
973 **mammals and teleosts.**

974 TAC peptides can act directly at different levels (hypothalamus, pituitary, and gastrointestinal
975 tract) to influence food intake and gut motility. In mammals (A), most of the available studies
976 report the stimulatory effects of tachykinins on gut motility. In teleosts (B), recent *in vitro*
977 studies are emerging, showing direct effects of TAC3 and TAC4 peptides on the expression of
978 neuropeptides highly expressed in the pituitary and that are involved in the central control of
979 food intake. These TAC peptides can also influence the expression of genes from the gut that
980 control its motility. For more details and for data from *in vivo* experiments, please refer to part 3
981 of this review. +, direct stimulatory effect; -, direct inhibitory effect; 0, no direct effect; AgRP,
982 agouti related peptide; CART, cocaine and amphetamine regulated transcript; CCK,
983 cholecystokinin; HK2, hemokinin 2; NKA, neurokinin A; NKB, neurokinin B; NMB, neuromedin
984 B; NPY, neuropeptide Y; POMC, proopiomelanocortin; PYY, peptide YY; SP, substance P.

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Table 1. *In vivo* studies concerning NKB action on gonadotropins in mammals and teleosts

Species	Sex	Age	Gonadal status	Treatment	Route	Effect	References
Mammals							
Human	Man	Adult		NKB	iv	None on LH-FSH release	Jayasena et al 2014
	Woman	Adult		NKB	iv	None on LH-FSH release	Jayasena et al 2014
	Man	Adult		NKB	iv	None on LH-FSH release	Narayanaswamy et al 2016
	Women	Adult		TACR3 antagonist	Orally	Inhibitory on LH release	Skorupskaite et al 2016
	Man	Adult		TACR3 antagonist	Orally	Inhibitory on LH-FSH release	Skorupskaite et al 2017
	Woman	Adult		TACR3 antagonist	Orally	Inhibitory on LH release	Skorupskaite et al 2018a
	Woman	Adult	Postmenopausal	TACR3 antagonist	Orally	Inhibitory on LH release None on FSH release	Skorupskaite et al 2018b
Rhesus monkey <i>Macaca mulatta</i>	Male	Juvenile	Agonadal	NKB Senktide	iv	Stimulatory on LH release	Ramaswamy et al 2010
Rhesus monkey	Male	Juvenile	Agonadal	Senktide	iv	Stimulatory on LH release	Ramaswamy et al 2011
Cynomolgus monkey <i>Macaca fascicularis</i>	Male	Adult	ORX	TACR3 antagonist	Orally	Inhibitory on LH-FSH release	Fraser et al 2015
Rat	Female	Adult	OVX	NKB	icv	None of LH release	Sahu and Kalra 1992
	Female	Adult	OVX+E2	Senktide	icv	Inhibitory LH release	Sandoval-Guzman et al 2004
	Female	Adult	Intact	Senktide	icv	Stimulatory on LH release	Navarro et al 2011a
			OVX+E2	Senktide	icv	Stimulatory on LH release	Navarro et al 2011a
			OVX+Sham	Senktide	icv	Inhibitory on LH release	Navarro et al 2011a
	Female	Prepubertal	Intact	Senktide	icv	Stimulatory on LH release	Navarro et al 2012
	Female	Adult	Intact	Senktide	icv	Stimulatory on LH release	Navarro et al 2012

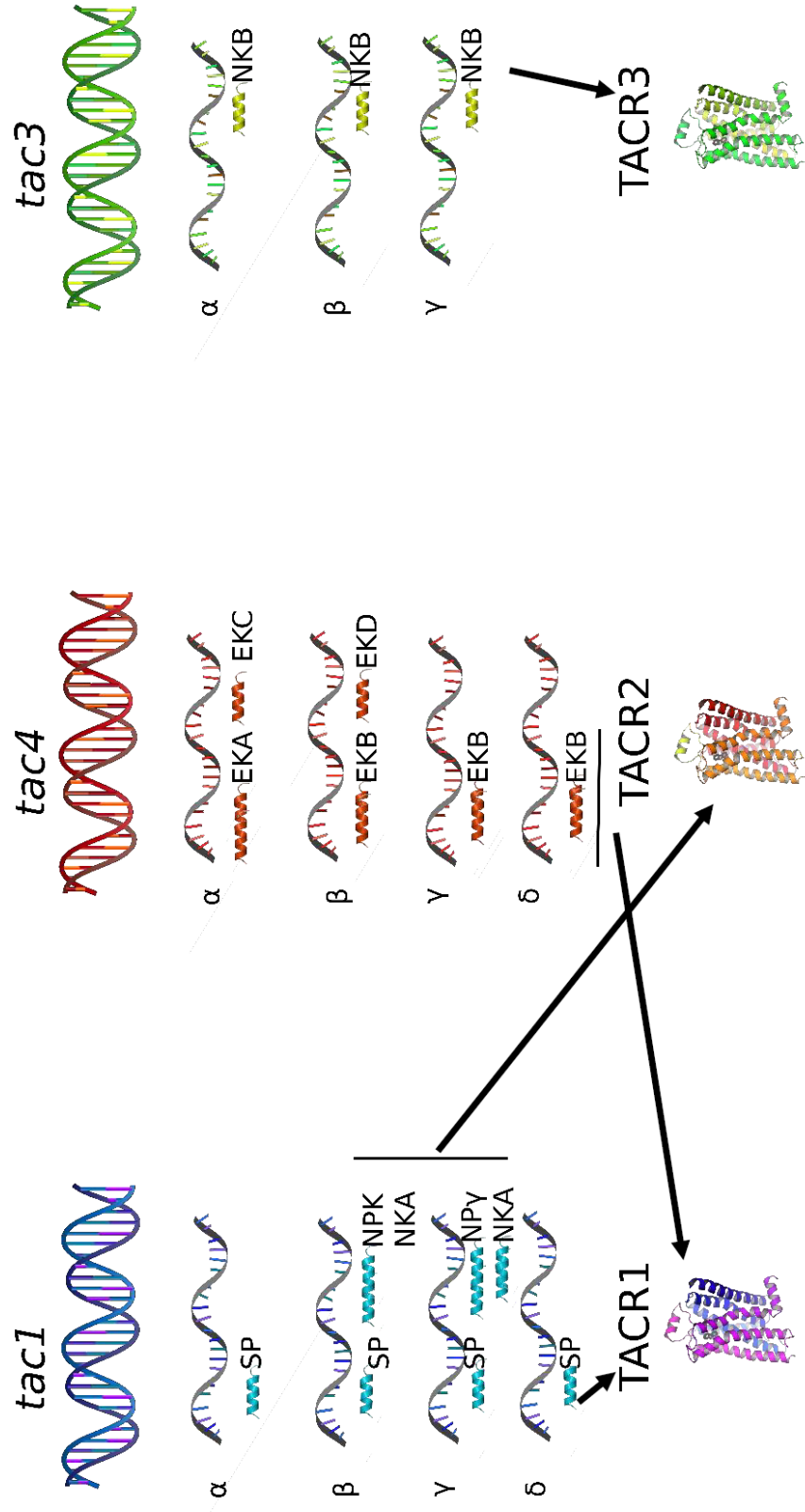
	Female	Prepubertal	Intact	TACR3 antagonist	icv	Decreasing trend on LH release	Navarro et al 2012
	Female	Adult	OVX	Senktide	icv	Inhibitory LH release	Kinsey-Jones et al 2012
		Adult	OVX+E2	Senktide	icv	Inhibitory LH release	Kinsey-Jones et al 2012
	Female	10-days	Intact	Senktide	icv	Stimulatory on LH release	Ruiz-Pino et al 2012
		25-days	Intact	Senktide	icv	Stimulatory on LH release	Ruiz-Pino et al 2012
		30-days	Intact	Senktide	icv	Stimulatory on LH release	Ruiz-Pino et al 2012
		36-days (Pubertal)	Intact	Senktide	icv	Stimulatory on LH release	Ruiz-Pino et al 2012
		Adult	Intact	Senktide	icv	Stimulatory on LH release	Ruiz-Pino et al 2012
		Adult	OVX+T	Senktide	icv	Stimulatory on LH release	Ruiz-Pino et al 2012
		Adult	OVX+Sham	Senktide	icv	None on LH release	Ruiz-Pino et al 2012
	Male	10-days	Intact	Senktide	icv	Stimulatory on LH release	Ruiz-Pino et al 2012
		25-days	Intact	Senktide	icv	Stimulatory on LH release	Ruiz-Pino et al 2012
		30-days	Intact	Senktide	icv	Stimulatory on LH release	Ruiz-Pino et al 2012
		45-days (Pubertal)	Intact	Senktide	icv	None on LH release	Ruiz-Pino et al 2012
		Adult	Intact	Senktide	icv	None on LH release	Ruiz-Pino et al 2012
		Adult	ORX+E2	Senktide	icv	None on LH release	Ruiz-Pino et al 2012
		Adult	ORX+Sham	Senktide	icv	Inhibitory on LH release	Ruiz-Pino et al 2012
	Female	Prepubertal	Intact	Senktide	icv	Stimulatory on LH release	Grachev et al 2012a
	Female	Adult	OVX+E2	Senktide	icv	Inhibitory on LH release	Grachev et al 2012b
		Adult	OVX+E2	Senktide +Antagonist	icv	Blockade of inhibitory on LH release	Grachev et al 2012b
	Female	10-days	Intact	Senktide	icv	Stimulatory on FSH release	Ruiz-Pino et al 2015
		25-days	Intact	Senktide	icv	Stimulatory on FSH release	Ruiz-Pino et al 2015
		36-days (Pubertal)	Intact	Senktide	icv	None on FSH release	Ruiz-Pino et al 2015
		Diestrus 1	Intact	Senktide	icv	None on FSH release	Ruiz-Pino et al 2015
		Proestrus	Intact	Senktide	icv	None on FSH release	Ruiz-Pino et al 2015
		Adult	OVX	Senktide	icv	None on FSH release	Ruiz-Pino et al 2015
	Male	10-days	Intact	Senktide	icv	Stimulatory on FSH release	Ruiz-Pino et al 2015

		25-days	Intact	Senktide	icv	None on FSH release	Ruiz-Pino et al 2015
		30-days	Intact	Senktide	icv	None on FSH release	Ruiz-Pino et al 2015
		45-days (Pubertal)	Intact	Senktide	icv	None on FSH release	Ruiz-Pino et al 2015
		Adult	Intact	Senktide	icv	None on FSH release	Ruiz-Pino et al 2015
		Adult	ORX	Senktide	icv	None on FSH release	Ruiz-Pino et al 2015
Mouse	Female	Adult	OVX+E2	Senktide	icv	None on LH release	Navarro et al 2009
		Adult	OVX+Sham	Senktide	icv	Inhibitory on LH release	Navarro et al 2009
	Male	Adult	Intact	NKB	ip	None on LH release	Corander et al 2010
	Male	Adult	Intact	Senktide	icv	Stimulatory on LH-FSH release	Navarro et al 2011b
	Male	Adult	Intact	Senktide	icv	Stimulatory on LH-FSH release	Navarro et al 2015
	Female	Adult	OVX+E2	Senktide	icv	Stimulatory on LH-FSH release	Navarro et al 2015
		Adult	OVX+Sham	Senktide	icv	Inhibitory on LH release	Navarro et al 2015
Sheep	Female	Adult	Anestrous	Senktide	icv	Stimulatory on LH release	Billings et al 2010
		Adult	Follicular phase	Senktide	icv	Stimulatory on LH release	Billings et al 2010
		Adult	Luteal phase	Senktide	icv	None on LH release	Billings et al 2010
	Female	Prepubertal		Senktide	iv	Stimulatory on LH release	Nestor et al 2012
	Female	Adult	Anestrous	NKB	icv	Stimulatory on LH release	Sakamoto et al 2012
	Female	Adult	OVX	TACR3 antagonist	Microim plants	Inhibitory on LH release	Goodman et al 2013
	Female	Adult	OVX	TACR3 antagonist	iv	Inhibitory on LH release = prolongs LH interpulse interval	Fraser et al 2015
	Female	Adult	Luteal phase	Senktide	icv	Stimulatory on LH release	Li et al 2015
			OVX	TACR3 antagonist	icv	Inhibitory on LH release	Li et al 2015
	Female	Fetal		Senktide	iv	Stimulatory on LH release	Amodei et al 2020
	Male	Fetal		Senktide	iv	Stimulatory on LH release	Amodei et al 2020
Cattle	Female		Lactating	Senktide	iv	Stimulatory on LH release	Nakamura et al 2017
Goat	Female	Adult	OVX	NKB	icv	None on LH release	Wakabayashi et al 2010

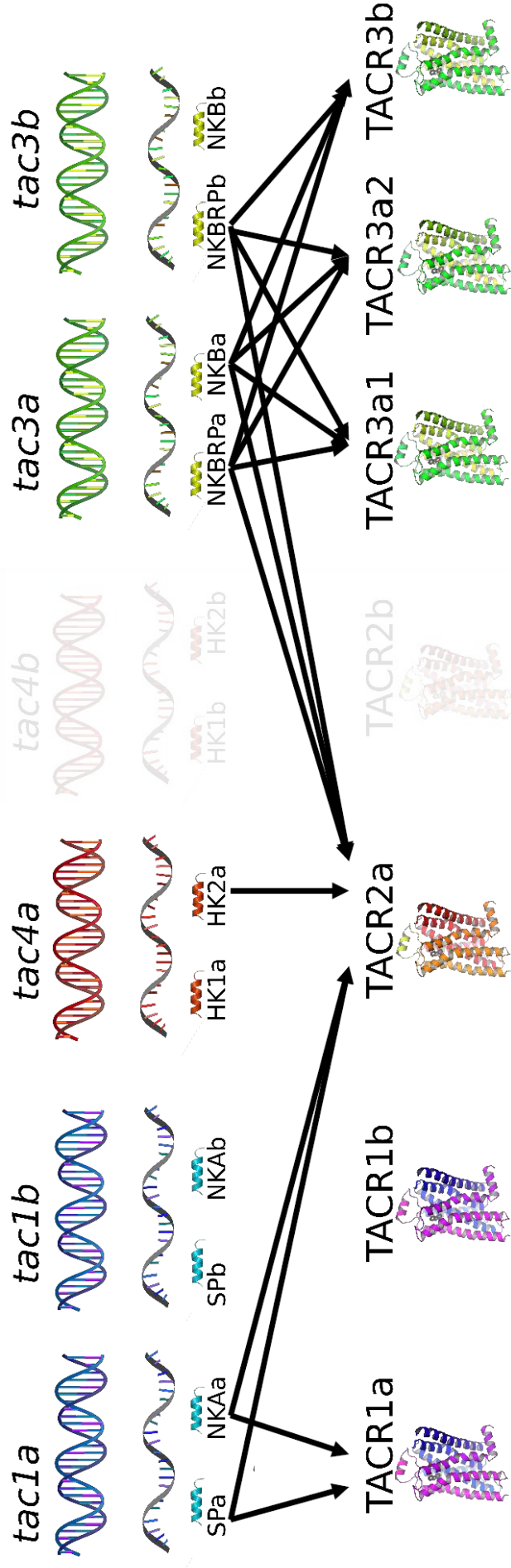
			OVX+E2	NKB	icv	None on LH release	Wakabayashi et al 2010
			OVX	Senktide	iv	Stimulatory on LH release	Yamamura et al 2015
			OVX+E2	Senktide	iv	Stimulatory on LH release	Yamamura et al 2015
Teleosts							
Zebrafish	Female	Adult	Mature	zfNKBa zfNKBb zfNKBRP (NKF)	ip	Stimulatory on LH release Stimulatory on LH release Stimulatory on LH release	Biran et al 2012
Tilapia	Male	Adult	Mature	tiNKB tiNKBRP (NKF)	ip	Stimulatory on LH-FSH release Stimulatory on LH release	Biran et al 2014
	Female	Adult	Mature	tiNKB tiNKBRP	ip	None on <i>lh-fsh</i> mRNAs None on <i>lh-fsh</i> mRNAs	Jin et al 2016
	Female	Adult	Mature	ti NKB tiNKBRP (NKF) NKB analog NKBRP analog	ip	Stimulatory on LH release Stimulatory on <i>lh-fsh</i> mRNAs Stimulatory on LH release None on <i>lh-fsh</i> mRNAs Stimulatory on LH-FSH release Stimulatory on <i>lh-fsh</i> mRNAs Stimulatory on LH-FSH release Stimulatory on <i>lh</i> mRNAs None on <i>fsh</i> mRNAs	Mizrahi et al 2019
Goldfish	Female	Adult Sexually immature	Early vitellogene sis	gfNKBa-10 gfNKBa-13	ip	Inhibitory on <i>lh-fsh</i> mRNAs Inhibitory on <i>lh-fsh</i> mRNAs	Liu et al 2019
			Mid- vitellogene sis	gfNKBa-10 gfNKBa-13 gfNKBb-11 gfNKBb-13	ip	Stimulatory on <i>lh</i> mRNAs None on <i>fsh</i> mRNAs Stimulatory on <i>lh-fsh</i> mRNAs None on <i>lh-fsh</i> mRNAs Stimulatory on <i>lh-fsh</i> mRNAs	Qi et al 2015
	Male	Adult Sexually immature	Early spermatog enesis	gfNKBa-10 gfNKBa-13	ip	Inhibitory on <i>lh-fsh</i> mRNAs Inhibitory on <i>lh</i> mRNAs None on <i>fsh</i> mRNAs	Liu et al 2019
			Late spermatog	gfNKBa-10 gfNKBa-13	ip	Stimulatory on <i>lh-fsh</i> mRNAs Stimulatory on <i>lh-fsh</i> mRNAs	Qi et al 2015

			genesis	gfNKCb-11 gfNKCb-13		None on <i>lh-fsh</i> mRNAs Stimulatory on <i>lh-fsh</i> mRNAs	
Orange-spotted grouper	Female	Adult	Early vitellogenesis	grouperNKB grouperNKBRP	ip ip	Stimulatory on <i>lh</i> mRNAs None on <i>fsh</i> mRNAs None on <i>lh-fsh</i> mRNAs	Chen et al 2018
Japanese eel	Female	Silver stage (prepubertal stage)	Immature	eelNKBa-10 eelNKBa-13 eelNKCb-10 eelNKCb-13	ip	Stimulatory on <i>lh</i> and <i>fsh</i> mRNAs None on <i>lh-fsh</i> mRNAs None on <i>lh-fsh</i> mRNAs Stimulatory <i>fsh</i> mRNAs None on <i>lh</i> mRNAs	Zuo et al 2022

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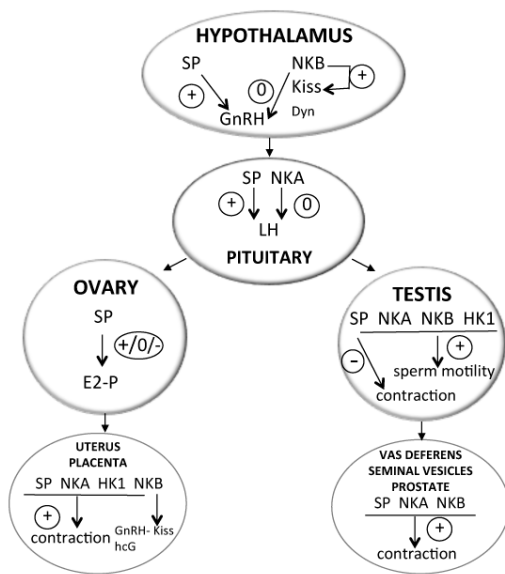


B



A)

MAMMALS



B)

TELEOSTS

