

# [Remarks on the prolactin hypothesis of peripartum cardiomyopathy](https://assignbuster.com/remarks-on-the-prolactin-hypothesis-of-peripartum-cardiomyopathy/)

[Health & Medicine](https://assignbuster.com/essay-subjects/health-n-medicine/)

A seminal study in 2007 introduced the hypothesis that an antiangiogenic prolactin fragment with a molecular mass of 16 kDa is a key pathological mediator of peripartum cardiomyopathy (PPCM) ( [1](#B1) ). The study reported that this fragment is enzymatically generated by the cleavage of full-length prolactin with the lysosomal aspartyl protease cathepsin D. Upon excessive generation, possibly due to high pituitary prolactin secretion near term or *postpartum* and an enhanced oxidative microenvironment, this prolactin fragment would impair myocardial microvascularization and thereby contribute to myocardial dysfunction. Accordingly, a new therapy for PPCM was explored using the dopamine D2 receptor agonists, cabergoline and bromocriptine. Treatment with bromocriptine is currently being evaluated in a multicenter clinical trial (NCT00998556) ( [2](#B2) ). The concept underlying this putative therapy is the inhibition of the generation of the prolactin fragment by substrate depletion, i. e., the inhibition of pituitary prolactin secretion by activation of dopamine D2 receptors in lactotropes. PPCM is a rare disease which occurred with a frequency of 1 case/3189 live births and an estimated mortality of 1. 36–2. 05% (confidence interval 0. 29–10. 8%) from 1990 to 2002 in the United States ( [3](#B3) ). However, the incidence of PPCM seems to be variable, depending on the geographical region, ethnic background, and other criteria ( [4](#B4) , [5](#B5) ).

Since the initial discovery, several research, case report, and review articles have been published ( [5](#B5) – [10](#B10) ) describing signaling mechanisms mediating the deleterious action of the 16-kDa prolactin fragment and supporting the beneficial effects of treatment with dopamine D2 agonists in patients with PPCM. However, there are relevant aspects to the proposed pathological mechanism in PPCM that are absent in these studies with the consequence of limiting the field by pointing to wrong, or incomplete conclusions.

In contrast to what is suggested in most of the PPCM-related literature, the 16-kDa prolactin fragment is only one of the several antiangiogenic prolactin fragments derived from prolactin *via* cathepsin D and other proteolytic enzymes. Altogether, these fragments of different molecular masses comprise a family of proteins termed vasoinhibins ( [11](#B11) , [12](#B12) ). Cathepsin D alone can generate four more vasoinhibins by cleaving full-length prolactin at sites other than the one generating the 16-kDa fragment ( [13](#B13) ). Three of these cathepsin D-generated vasoinhibin isoforms have documented antiangiogenic activity ( [11](#B11) , [13](#B13) )—a notion that should not go unnoticed when studying the 16-kDa vasoinhibin isoform as a key pathologic mediator of PPCM. The possible contribution of other vasoinhibin isoforms to the pathophysiology of PPCM has neither been investigated nor discussed, not to mention the vasoinhibin isoforms generated by other proteolytic enzymes up regulated in experimental PPCM, such as matrix metalloproteinases ( [1](#B1) , [11](#B11) ).

The term “ 16 kDa PRL” (referring to prolactin as the precursor of the fragment) that has often been used in the PPCM-related literature was updated by the vasoinhibin nomenclature in 2006 ( [11](#B11) , [12](#B12) , [14](#B14) ), and this nomenclature has been refined and reevaluated since then ( [15](#B15) – [17](#B17) ). The introduction of the vasoinhibin nomenclature was triggered by the recognition that the 16-kDa fragment is not the only endogenous prolactin fragment with antiangiogenic properties. As their functional and structural features are unique and contrast with those of full-length prolactin, it was recognized that these fragments are individual hormones and may not bear the same designation. In consequence they were collectively named “ vasoinhibins,” inspired by one of their principal effects, the inhibition of blood vessel growth, and control of blood vessel function.

Another neglected issue concerns the levels of vasoinhibins and the total composition of their isoforms in the circulation during healthy and disease states. In the absence of a quantitative vasoinhibin assay, neither reference ranges nor levels in disease states could be established. Yet, this is required to confirm the contribution of the 16-kDa vasoinhibin isoform to the pathophysiology of PPCM. Higher levels of 16-kDa vasoinhibin would be expected at the onset and declining levels during regression of PPCM. This also concerns the safety of using dopamine agonists to inhibit the generation of vasoinhibins. It should be acknowledged that inhibiting vasoinhibin generation constitutes an intervention into a complex endocrine axis [the prolactin/vasoinhibin axis ( [18](#B18) )], which could lead to unintended side effects. Some of the cardiovascular side effects of bromocriptine such as syncope, hypotension, and pleural/pericardial effusion could be influenced by a decline of vasoinhibin levels. This is a possibility as vasoinhibins feature inhibition of vasodilation and vasopermeability ( [15](#B15) , [16](#B16) , [18](#B18) ).

We suggest that whenever the role of the vasoinhibins in PPCM is investigated, their serum levels should be evaluated. This is possible by an established methodology combining immunoprecipitation and western blotting (semi-quantitative) ( [19](#B19) ). Ideally, at some point in the future, a quantitative vasoinhibin assay could be developed which should then be used to confirm altered levels of vasoinhibin isoforms in PPCM. Although dopamine agonists have been used during pregnancy, the safety of this intervention should carefully be monitored. This is particularly relevant on the background that vasoinhibins are pleiotropic hormones which control angiogenesis-mediated growth in reproductive and non-reproductive organs ( [18](#B18) ); regulate blood vessel growth, vasopermeability, and vasodilation ( [15](#B15) , [16](#B16) ); and have non-vascular effects, which include stimulation of vasopressin release ( [20](#B20) ), thrombolytic effects ( [21](#B21) ), and the stimulation of anxiety- and depression-related behaviors ( [22](#B22) ).

## Author Contributions

JT drafted the manuscript. CC, GE, and TB revised the manuscript.

## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References

1. Hilfiker-Kleiner D, Kaminski K, Podewski E, Bonda T, Schaefer A, Sliwa K, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. *Cell* (2007) 128(3): 589–600. doi: 10. 1016/j. cell. 2006. 12. 036

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17289576) | [CrossRef Full Text](https://doi.org/10.1016/j.cell.2006.12.036) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=A+cathepsin+D-cleaved+16+kDa+form+of+prolactin+mediates+postpartum+cardiomyopathy&author=D.+Hilfiker-Kleiner&author=K.+Kaminski&author=E.+Podewski&author=T.+Bonda&author=A.+Schaefer&author=K.+Sliwa&journal=Cell&publication_year=2007&volume=128&pages=589–600&doi=10.1016/j.cell.2006.12.036&pmid=17289576)

2. Haghikia A, Podewski E, Berliner D, Sonnenschein K, Fischer D, Angermann CE, et al. Rationale and design of a randomized, controlled multicentre clinical trial to evaluate the effect of bromocriptine on left ventricular function in women with peripartum cardiomyopathy. *Clin Res Cardiol* (2015) 104(11): 911–7. doi: 10. 1007/s00392-015-0869-5

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26026286) | [CrossRef Full Text](https://doi.org/10.1007/s00392-015-0869-5) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Rationale+and+design+of+a+randomized,+controlled+multicentre+clinical+trial+to+evaluate+the+effect+of+bromocriptine+on+left+ventricular+function+in+women+with+peripartum+cardiomyopathy&author=A.+Haghikia&author=E.+Podewski&author=D.+Berliner&author=K.+Sonnenschein&author=D.+Fischer&author=C.+E.+Angermann&journal=Clin+Res+Cardiol&publication_year=2015&volume=104&pages=911–7&doi=10.1007/s00392-015-0869-5&pmid=26026286)

3. Mielniczuk LM, Williams K, Davis DR, Tang AS, Lemery R, Green MS, et al. Frequency of peripartum cardiomyopathy. *Am J Cardiol* (2006) 97(12): 1765–8. doi: 10. 1016/j. amjcard. 2006. 01. 039

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16765131) | [CrossRef Full Text](https://doi.org/10.1016/j.amjcard.2006.01.039) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Frequency+of+peripartum+cardiomyopathy&author=L.+M.+Mielniczuk&author=K.+Williams&author=D.+R.+Davis&author=A.+S.+Tang&author=R.+Lemery&author=M.+S.+Green&journal=Am+J+Cardiol&publication_year=2006&volume=97&pages=1765–8&doi=10.1016/j.amjcard.2006.01.039&pmid=16765131)

4. Brar SS, Khan SS, Sandhu GK, Jorgensen MB, Parikh N, Hsu JW, et al. Incidence, mortality, and racial differences in peripartum cardiomyopathy. *Am J Cardiol* (2007) 100(2): 302–4. doi: 10. 1016/j. amjcard. 2007. 02. 092

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17631087) | [CrossRef Full Text](https://doi.org/10.1016/j.amjcard.2007.02.092) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Incidence,+mortality,+and+racial+differences+in+peripartum+cardiomyopathy&author=S.+S.+Brar&author=S.+S.+Khan&author=G.+K.+Sandhu&author=M.+B.+Jorgensen&author=N.+Parikh&author=J.+W.+Hsu&journal=Am+J+Cardiol&publication_year=2007&volume=100&pages=302–4&doi=10.1016/j.amjcard.2007.02.092&pmid=17631087)

5. Hilfiker-Kleiner D, Sliwa K. Pathophysiology and epidemiology of peripartum cardiomyopathy. *Nat Rev Cardiol* (2014) 11(6): 364–70. doi: 10. 1038/nrcardio. 2014. 37

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24686946) | [CrossRef Full Text](https://doi.org/10.1038/nrcardio.2014.37) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Pathophysiology+and+epidemiology+of+peripartum+cardiomyopathy&author=D.+Hilfiker-Kleiner&author=K.+Sliwa&journal=Nat+Rev+Cardiol&publication_year=2014&volume=11&pages=364–70&doi=10.1038/nrcardio.2014.37&pmid=24686946)

6. Halkein J, Tabruyn SP, Ricke-Hoch M, Haghikia A, Nguyen NQ, Scherr M, et al. microRNA-146a is a therapeutic target and biomarker for peripartum cardiomyopathy. *J Clin Invest* (2013) 123(5): 2143–54. doi: 10. 1172/JCI64365

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23619365) | [CrossRef Full Text](https://doi.org/10.1172/JCI64365) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=microRNA-146a+is+a+therapeutic+target+and+biomarker+for+peripartum+cardiomyopathy&author=J.+Halkein&author=S.+P.+Tabruyn&author=M.+Ricke-Hoch&author=A.+Haghikia&author=N.+Q.+Nguyen&author=M.+Scherr&journal=J+Clin+Invest&publication_year=2013&volume=123&pages=2143–54&doi=10.1172/JCI64365&pmid=23619365)

7. Melo MA, Carvalho JS, Feitosa FE, Araujo Junior E, Peixoto AB, Costa Carvalho FH, et al. Peripartum cardiomyopathy treatment with dopamine agonist and subsequent pregnancy with a satisfactory outcome. *Rev Bras Ginecol Obstet* (2016) 38(6): 308–13. doi: 10. 1055/s-0036-1584567

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27399926) | [CrossRef Full Text](https://doi.org/10.1055/s-0036-1584567) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Peripartum+cardiomyopathy+treatment+with+dopamine+agonist+and+subsequent+pregnancy+with+a+satisfactory+outcome&author=M.+A.+Melo&author=J.+S.+Carvalho&author=F.+E.+Feitosa&author=E.+Araujo+Junior&author=A.+B.+Peixoto&author=F.+H.+Costa+Carvalho&journal=Rev+Bras+Ginecol+Obstet&publication_year=2016&volume=38&pages=308–13&doi=10.1055/s-0036-1584567&pmid=27399926)

8. Arany Z, Elkayam U. Peripartum cardiomyopathy. *Circulation* (2016) 133(14): 1397–409. doi: 10. 1161/CIRCULATIONAHA. 115. 020491

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27045128) | [CrossRef Full Text](https://doi.org/10.1161/CIRCULATIONAHA.115.020491) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Peripartum+cardiomyopathy&author=Z.+Arany&author=U.+Elkayam&journal=Circulation&publication_year=2016&volume=133&pages=1397–409&doi=10.1161/CIRCULATIONAHA.115.020491&pmid=27045128)

9. Bello NA, Arany Z. Molecular mechanisms of peripartum cardiomyopathy: a vascular/hormonal hypothesis. *Trends Cardiovasc Med* (2015) 25(6): 499–504. doi: 10. 1016/j. tcm. 2015. 01. 004

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25697684) | [CrossRef Full Text](https://doi.org/10.1016/j.tcm.2015.01.004) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Molecular+mechanisms+of+peripartum+cardiomyopathy:+a+vascular/hormonal+hypothesis&author=N.+A.+Bello&author=Z.+Arany&journal=Trends+Cardiovasc+Med&publication_year=2015&volume=25&pages=499–504&doi=10.1016/j.tcm.2015.01.004&pmid=25697684)

10. Bernard V, Young J, Chanson P, Binart N. New insights in prolactin: pathological implications. *Nat Rev Endocrinol* (2015) 11(5): 265–75. doi: 10. 1038/nrendo. 2015. 36

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25781857) | [CrossRef Full Text](https://doi.org/10.1038/nrendo.2015.36) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=New+insights+in+prolactin:+pathological+implications&author=V.+Bernard&author=J.+Young&author=P.+Chanson&author=N.+Binart&journal=Nat+Rev+Endocrinol&publication_year=2015&volume=11&pages=265–75&doi=10.1038/nrendo.2015.36&pmid=25781857)

11. Macotela Y, Aguilar MB, Guzman-Morales J, Rivera JC, Zermeno C, Lopez-Barrera F, et al. Matrix metalloproteases from chondrocytes generate an antiangiogenic 16 kDa prolactin. *J Cell Sci* (2006) 119(Pt 9): 1790–800. doi: 10. 1242/jcs. 02887

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16608881) | [CrossRef Full Text](https://doi.org/10.1242/jcs.02887) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Matrix+metalloproteases+from+chondrocytes+generate+an+antiangiogenic+16+kDa+prolactin&author=Y.+Macotela&author=M.+B.+Aguilar&author=J.+Guzman-Morales&author=J.+C.+Rivera&author=C.+Zermeno&author=F.+Lopez-Barrera&journal=J+Cell+Sci&publication_year=2006&volume=119&pages=1790–800&doi=10.1242/jcs.02887&pmid=16608881)

12. Clapp C, Aranda J, Gonzalez C, Jeziorski MC, Martinez de la Escalera G. Vasoinhibins: endogenous regulators of angiogenesis and vascular function. *Trends Endocrinol Metab* (2006) 17(8): 301–7. doi: 10. 1016/j. tem. 2006. 08. 002

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16934485) | [CrossRef Full Text](https://doi.org/10.1016/j.tem.2006.08.002) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Vasoinhibins:+endogenous+regulators+of+angiogenesis+and+vascular+function&author=C.+Clapp&author=J.+Aranda&author=C.+Gonzalez&author=M.+C.+Jeziorski&author=G.+Martinez+de+la+Escalera&journal=Trends+Endocrinol+Metab&publication_year=2006&volume=17&pages=301–7&doi=10.1016/j.tem.2006.08.002&pmid=16934485)

13. Piwnica D, Touraine P, Struman I, Tabruyn S, Bolbach G, Clapp C, et al. Cathepsin D processes human prolactin into multiple 16K-like N-terminal fragments: study of their antiangiogenic properties and physiological relevance. *Mol Endocrinol* (2004) 18(10): 2522–42. doi: 10. 1210/me. 2004-0200

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15192082) | [CrossRef Full Text](https://doi.org/10.1210/me.2004-0200) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Cathepsin+D+processes+human+prolactin+into+multiple+16K-like+N-terminal+fragments:+study+of+their+antiangiogenic+properties+and+physiological+relevance&author=D.+Piwnica&author=P.+Touraine&author=I.+Struman&author=S.+Tabruyn&author=G.+Bolbach&author=C.+Clapp&journal=Mol+Endocrinol&publication_year=2004&volume=18&pages=2522–42&doi=10.1210/me.2004-0200&pmid=15192082)

14. Clapp C, Gonzalez C, Macotela Y, Aranda J, Rivera JC, Garcia C, et al. Vasoinhibins: a family of N-terminal prolactin fragments that inhibit angiogenesis and vascular function. *Front Horm Res* (2006) 35: 64–73. doi: 10. 1159/000094309

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16809923) | [CrossRef Full Text](https://doi.org/10.1159/000094309) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Vasoinhibins:+a+family+of+N-terminal+prolactin+fragments+that+inhibit+angiogenesis+and+vascular+function&author=C.+Clapp&author=C.+Gonzalez&author=Y.+Macotela&author=J.+Aranda&author=J.+C.+Rivera&author=C.+Garcia&journal=Front+Horm+Res&publication_year=2006&volume=35&pages=64–73&doi=10.1159/000094309&pmid=16809923)

15. Clapp C, Thebault S, Macotela Y, Moreno-Carranza B, Triebel J, Martinez de la Escalera G. Regulation of blood vessels by prolactin and vasoinhibins. *Adv Exp Med Biol* (2015) 846: 83–95. doi: 10. 1007/978-3-319-12114-7\_4

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25472535) | [CrossRef Full Text](https://doi.org/10.1007/978-3-319-12114-7_4) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Regulation+of+blood+vessels+by+prolactin+and+vasoinhibins&author=C.+Clapp&author=S.+Thebault&author=Y.+Macotela&author=B.+Moreno-Carranza&author=J.+Triebel&author=G.+Martinez+de+la+Escalera&journal=Adv+Exp+Med+Biol&publication_year=2015&volume=846&pages=83–95&doi=10.1007/978-3-319-12114-7_4&pmid=25472535)

16. Clapp C, Thebault S, Jeziorski MC, Martinez De La Escalera G. Peptide hormone regulation of angiogenesis. *Physiol Rev* (2009) 89(4): 1177–215. doi: 10. 1152/physrev. 00024. 2009

[CrossRef Full Text](https://doi.org/10.1152/physrev.00024.2009) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Peptide+hormone+regulation+of+angiogenesis&author=C.+Clapp&author=S.+Thebault&author=M.+C.+Jeziorski&author=G.+Martinez+De+La+Escalera&journal=Physiol+Rev&publication_year=2009&volume=89&pages=1177–215&doi=10.1152/physrev.00024.2009)

17. Triebel J, Bertsch T, Martinez de la Escalera G, Clapp C. On the path toward classifying hormones of the vasoinhibin-family. *Front Endocrinol* (2015) 6: 16. doi: 10. 3389/fendo. 2015. 00016

[CrossRef Full Text](https://doi.org/10.3389/fendo.2015.00016) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=On+the+path+toward+classifying+hormones+of+the+vasoinhibin-family&author=J.+Triebel&author=T.+Bertsch&author=G.+Martinez+de+la+Escalera&author=C.+Clapp&journal=Front+Endocrinol&publication_year=2015&volume=6&pages=16&doi=10.3389/fendo.2015.00016)

18. Triebel J, Bertsch T, Bollheimer C, Rios-Barrera D, Pearce CF, Hufner M, et al. Principles of the prolactin/vasoinhibin axis. *Am J Physiol Regul Integr Comp Physiol* (2015) 309(10): R1193–203. doi: 10. 1152/ajpregu. 00256. 2015

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26310939) | [CrossRef Full Text](https://doi.org/10.1152/ajpregu.00256.2015) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Principles+of+the+prolactin/vasoinhibin+axis&author=J.+Triebel&author=T.+Bertsch&author=C.+Bollheimer&author=D.+Rios-Barrera&author=C.+F.+Pearce&author=M.+Hufner&journal=Am+J+Physiol+Regul+Integr+Comp+Physiol&publication_year=2015&volume=309&pages=R1193–203&doi=10.1152/ajpregu.00256.2015&pmid=26310939)

19. Gonzalez C, Parra A, Ramirez-Peredo J, Garcia C, Rivera JC, Macotela Y, et al. Elevated vasoinhibins may contribute to endothelial cell dysfunction and low birth weight in preeclampsia. *Lab Invest* (2007) 87(10): 1009–17. doi: 10. 1038/labinvest. 3700662

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17676064) | [CrossRef Full Text](https://doi.org/10.1038/labinvest.3700662) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Elevated+vasoinhibins+may+contribute+to+endothelial+cell+dysfunction+and+low+birth+weight+in+preeclampsia&author=C.+Gonzalez&author=A.+Parra&author=J.+Ramirez-Peredo&author=C.+Garcia&author=J.+C.+Rivera&author=Y.+Macotela&journal=Lab+Invest&publication_year=2007&volume=87&pages=1009–17&doi=10.1038/labinvest.3700662&pmid=17676064)

20. Mejia S, Torner LM, Jeziorski MC, Gonzalez C, Morales MA, de la Escalera GM, et al. Prolactin and 16K prolactin stimulate release of vasopressin by a direct effect on hypothalamo-neurohypophyseal system. *Endocrine* (2003) 20(1–2): 155–62. doi: 10. 1385/ENDO: 20: 1-2: 155

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12668881) | [CrossRef Full Text](https://doi.org/10.1385/ENDO%3A%2020%3A%201-2%3A%20155) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Prolactin+and+16K+prolactin+stimulate+release+of+vasopressin+by+a+direct+effect+on+hypothalamo-neurohypophyseal+system&author=S.+Mejia&author=L.+M.+Torner&author=M.+C.+Jeziorski&author=C.+Gonzalez&author=M.+A.+Morales&author=G.+M.+de+la+Escalera&journal=Endocrine&publication_year=2003&volume=20&pages=155–62&doi=10.1385/ENDO: 20: 1-2: 155&pmid=12668881)

21. Bajou K, Herkenne S, Thijssen VL, D’Amico S, Nguyen NQ, Bouche A, et al. PAI-1 mediates the antiangiogenic and profibrinolytic effects of 16K prolactin. *Nat Med* (2014) 20(7): 741–7. doi: 10. 1038/nm. 3552

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24929950) | [CrossRef Full Text](https://doi.org/10.1038/nm.3552) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=PAI-1+mediates+the+antiangiogenic+and+profibrinolytic+effects+of+16K+prolactin&author=K.+Bajou&author=S.+Herkenne&author=V.+L.+Thijssen&author=S.+D’Amico&author=N.+Q.+Nguyen&author=A.+Bouche&journal=Nat+Med&publication_year=2014&volume=20&pages=741–7&doi=10.1038/nm.3552&pmid=24929950)

22. Zamorano M, Ledesma-Colunga MG, Adan N, Vera-Massieu C, Lemini M, Mendez I, et al. Prolactin-derived vasoinhibins increase anxiety- and depression-related behaviors. *Psychoneuroendocrinology* (2014) 44: 123–32. doi: 10. 1016/j. psyneuen. 2014. 03. 006

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24767626) | [CrossRef Full Text](https://doi.org/10.1016/j.psyneuen.2014.03.006) | [Google Scholar](http://scholar.google.com/scholar_lookup?title=Prolactin-derived+vasoinhibins+increase+anxiety-+and+depression-related+behaviors&author=M.+Zamorano&author=M.+G.+Ledesma-Colunga&author=N.+Adan&author=C.+Vera-Massieu&author=M.+Lemini&author=I.+Mendez&journal=Psychoneuroendocrinology&publication_year=2014&volume=44&pages=123–32&doi=10.1016/j.psyneuen.2014.03.006&pmid=24767626)