Human and animal behavioural change with nonapeptide agonists and antagonists

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‘Sociality’ oligopeptides

Vasotocin is an oligopeptide hybride of oxytocin and vasopressin found in all non-mammalian vertebrates including birds, fish, amphibans and in fetal mammals. In mammals it appears to have similar biological properties to both oxytocin (stimulating reproductive tract contraction as in egg laying or birth) and vasopressin (diuretic and antidiuretic effects).

It has been found to have effects on the regulation of REM sleep.

Arginine vasopressin (AVP) and oxytocin (OXT), comprise neuroendocrine circuits that range from being evolutionarily conserved to evolutionarily diverse.

http://en.wikipedia.org/wiki/Vasotocin http://www.ncbi.nlm.nih.gov/pubmed/18655867 http://www.ncbi.nlm.nih.gov/pubmed/10964521

Nonapeptides

Relative weighting of hypothalamic and BSTm nonapeptide circuitries may be an important determinant of approach-avoidance behaviour, and may be a prime target of natural selection related to sociality pressin and oxitocin receptors are located in several places of the animal and human body

http://www.ncbi.nlm.nih.gov/pubmed/18655867

Vasopressin and oxitocin receptors

Vasopressin and oxitocin receptors are located in several places of the animal and human body

The chemical structure of the receptors are different

They play a role in very different regulatory processes

Receptor family

Vasopressin receptors belong to the GTP binding G-protein-coupled trans-membrane receptor family that activates phospholipases via Gq/11

Birnbaumer, M. (2000) Vasopressin receptors. Trends Endocrinol. Metab. 11, 406–410.

Oxytocin receptor is a class I G protein-coupled transmembrane receptor that is primarily coupled via Gq proteins to phospholipase C-β

Gimpl G, Fahrenholz F. (2001) The Oxytocin Receptor System: Structure, Function, and Regulation. Physiol Rev April 2001 vol. 81 no. 2 629-683

V1a (vascular) / V2 (renal) receptor subtypes

V1a receptor subtypes

Location: brain

Agonists: promote aggressive behavior

Antagonist: SRX251 (Azevan): selectively blocks aggressive behavior
http://www.ncbi.nlm.nih.gov/pubmed/16504276

CNS-penetrating, promising pipeline product

Treatment of interpersonal violence co-occurring with such illness as ADHD, PTSD, autism, bipolar disorder, and substance abuse, selectively block stress, arousal, and fear in social interaction models without impacting other behaviors

ADHD = attention deficit hyperactivity disorder;

PTSD = post-traumatic stress disorder

Location: vascular smooth muscle cells, collecting tubules of kidney, cardiomyocytes, hepatocytes, platelets, brain, testis

Agonists: antidiuretic action of vasopressin, vasosopasm, coronary vasospasm, positiv inotropy, hypertension, glycogen metabolism, platelet aggregation, vascular smooth muscle proliferation, aggressive behavior

Antagonists: aquaresis with increased serum Na+ concentration and reduced cardiac preload. Some effectiveness in Raynaud's disease, dysmenorrhea, and preterm labor

Treatment of water retaining diseases, heart failure, hyponatraemia, hypertension, **SIADH** (=inappropriate ADH secretion syndrome)

Antagonists: Conivaptan, lixivaptan and tolvaptan (non-peptide inhibitor of ADH, vasopressin receptor antagonist).

Conivaptan: Approved for treatment of hyponatraemia caused by **SIADH** (marketed by Astellas)

Lixivaptan: Phase III for treatment of **cirrhosis and dilutional hyponatraemia**

Tolvaptan: Phase III as aquaretic agent in **advanced heart failure syndromes**

Water drinking in dehydration

Vasopressin secretion in response to dehydration or hypertonic saline loading is disrupted in mice lacking **secretin** or its receptor. The data suggest that brain-generated secretin may play a role in neural pathways regulating fluid balance.

http://f1000.com/10505956

V2 receptors

Other possible roles in therapy:

Type II Diabetes

Islet function is regulated by a number of different signals. A main signal is generated by glucose, which stimulates insulin secretion and inhibits glucagon secretion.

The glucose effects are modulated by many factors, including hormones, neurotransmitters and nutrients. Several of these factors signal through (G protein)-coupled receptors (GPCR).

Both systemic **secretin** and **oxytocin** are involved in regulating gastrointestinal functions and natriuresis, systemically released secretin might act partly through oxytocin. Vasopressin may play a role too.

http://www.mendeley.com/research/molecular-cloning-expression-cdna-encoding-secretin-receptor/

http://www.mendeley.com/research/molecular-cloning-functional-expression-cdna-encoding-human-v1b-vasopressin-receptor/

http://endo.endojournals.org/content/151/6/2681.full

http://www.ncbi.nlm.nih.gov/pubmed/11174021

Diabetes insipidus

Diabetes insipidus may develop secondary to vasopressin deficiency.

http://www.ncbi.nlm.nih.gov/pubmed/11167932

V1b / v3 receptor subtypes

Location: brain, neocortex, hypothalamus, hypothalamic paraventricular nucleus, anterior pituitary, hyppocampus, amygdala, suprachiasmatic nucleus, tegmentum, substantia nigra, area postrema, olfactory bulb,

http://edoc.ub.uni-muenchen.de/9109/1/Bunck_Mirjam.pdf

spinal cord, endothelial cells, Langerhans islets, adrenal medulla, kidney

Genetic polymorphism: several genetic polymorhisms have been identified that are likely to play a critical role in the under-expression of vasopressin in certain animals and in the development of anxiety and depression; epigenetic factors are also important

http://edoc.ub.uni-muenchen.de/9109/1/Bunck_Mirjam.pdf

http://endo.endojournals.org/content/138/10/4109.full.pdf

Agonists: release of ACTH, glucagon secretion, modulation of emotional processes

Agonists: V1b receptors mediate the transition to excessive drinking in ethanol-dependent rats (amygdala)

Antagonist SSR149415: selective v3 antagonist, completely blocked hyperalgesic responses during colorectal distension stress
http://www.ncbi.nlm.nih.gov/pubmed/19033533

and blocked aggressive behaviors in hamsters using a resident-intruder paradigm
http://ggriebel.chez-alice.fr/Pub82.pdf

But a phase II trial failed with this agent for treatment of depression and anxiety (2009)

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3016603/

Benzazepines: Tricyclic diazepine vasopressin antagonists and oxytocin antagonists, peripheral-type: inhibited dopamin release from PC12 pheochromocytoma cells

Central-type benzodiazepine receptors mediate the antidopaminergic effect of clonazepam and melatonin in 6-hydroxydopamine lesioned rats, there is involvement of a GABAergic mechanism

http://jpet.aspetjournals.org/content/274/1/84

Antagonist SSR149415: It has also been radiolabelled with tritium and used in receptor autoradiography to reveal low-resolution binding in the human and rat pituitary — no Avpr1b (arginine vasopressin receptor 1B) binding sites were observed in sections of rat brain

Serradeil-Le Gal et al. 2007

Recently, SSR149415 has failed phase II clinical trials

http://informahealthcare.com/doi/abs/10.1517/13543780903184591
http://www.ncbi.nlm.nih.gov/pubmed/19715445

Overall, the results of studies with SSR149415 evidence a possible role for the Avpr1b (arginine vasopressin receptor 1B) in affective disorders and point to animal model-validated targets with which to treat them

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3016603/

A summary of 38 studies conducted with Avprlb antagonists on behaviour is given in Roper et al. (2010):

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3016603/

Aggression	↓	Anxiety	↓	Conflict	↓
Depression	↓				
Hyperalgesia	↓	Hyperactivity	↓		
Offensive	↓				
Seeking Alcohol	↓	Seeking Heroin	↓		
Social interaction	↓	Social motivation	↓		

↓ denotes **decreased** behavioural phenotype in animals

Agonists: d[Leu4, Lys8]Vasopressin, a V1b-Selective Agonist for Rat Vasopressin/Oxytocin Receptor.

In high doses it is anti-diuretic, vasopressor, and *in vitro* oxytocic activities were weak compared with those of VP.

In contrast, used at low doses, its efficiency to stimulate adrenocorticotropin or insulin release from mouse pituitary or perfused rat pancreas, respectively, was similar to that obtained with VP

http://endo.endojournals.org/content/148/9/4136

'Contradictory' results suggest that dose-dependency is very important in understanding the effect of Vasopressin and it should be carefully studied experimentally!

V1b / v3 and OXT receptors

Other possible roles in behavioral change:

Generosity and altruistic behavior AVPR1A (arginine vasopressin receptor 1A) is the "*ruthlessness gene*"

http://www.nature.com/news/2008/080404/full/news.2008.738.html

The injection of oxytocin (OXT) vs. oxytocin antagonist (OTA) at birth has sexually dimorphic effects in prairie voles later on in life in various areas of the brain ttp://www.sciencedirect.com/science/article/pii/S0306452206012358

It is not known yet whether this result is 'translational' to other mammals or not?

Male knockout mice in Avpr1a (arginine vasopressin receptor 1A) have

- reduced anxiety-like behavior,
- greatly impaired social recognition abilities,
- deficits in circadian rhythms and
- deficits in olfaction

Other possible roles in behavioral change:

Promiscuous voles have fewer vaso-pressin (V1a) receptors in the ventral forebrain

http://news.bbc.co.uk/2/hi/science/nature/3812483.stm

http://www.thefreelibrary.com/Hormone+of+monogamy%3A+the+prairie+vole+and+the+biology+of+mating.-a014642472

V1b / v3 and pair-bonding

Fewer than 5% of mammals are habitually monogamous. Prairie voles (*Microtus ochrogaster*) are among the select few. Prairie voles are generally monogamous

Mountain voles are generally polygamous

Vasopressin receptors in brain may be responsible for this phenomenon
http://www.pnas.org/content/89/13/5981.full.pdf

Research indicates that vasopressin induces the male prairie vole to stay with and protect his mate and the father prairie vole caring for his pups

Neuroscientists believe that a chemical produced in the brain may turn on monogamous behavior.

http://news.bbc.co.uk/2/hi/science/nature/3812483.stm
http://www.pnas.org/content/106/45/19144.full

V1b / v3 and OXT receptors

Other possible roles in behavioral change:

Autism link. Two studies have already found there is a modest link between vasopressin and autism

http://news.bbc.co.uk/2/hi/science/nature/3812483.stm
http://www.biologicalpsychiatryjournal.com/article/S0006-3223(98)00142-5/abstract

Autism link. Recently oxytocin therapy is used for social deficits in autism and schizophrenia

http://www.ncbi.nlm.nih.gov/pubmed/21325177

Oxytocin and vasopressin may play a role in social brain development and the pathogenesis and therapy of autism

http://www.ncbi.nlm.nih.gov/pubmed/19335381

http://www.usc.edu/uscnews/stories/13992.html

Anorgasmy therapy

Changes in oxytocin and vasopressin secretion has been proved during sexual activity in men.

Murphy MR et al. (1987)Changes in oxytocin and vasopressin secretion during sexual activity in men. J Clin Endocrinol Metab 65:738–741.

http://www.ncbi.nlm.nih.gov/pubmed/2401707

http://physrev.physiology.org/content/81/2/629.full

V1b / v3 receptors

Other possible roles in therapy:

Fever therapy

The antipyretic effect of arginine vasopressin (AVP) introduced into the brain by push-pull perfusion was investigated in the sheep. Sucrose solutions containing AVP (4.0 microgram/ml.) perfused at 40 microliter./min had significant antipyretic activity, but had no effect on resting body temperature. Loci in which AVP induced antipyresis were limited to the septal region about 2-3 mm anterior to the anterior commissure. AVP administered I.V. did not lower fever.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1278785/

http://www.jneurosci.org/content/24/9/2226.full.pdf

Possible roles of Avprlb antagonists in therapy in men (Summary):

Possible roles of Avprlb antagonists in therapy in men:

Substance abuse, addictions (Alcoholism, Heroinism therapy)

Fever therapy

Anorgasmy

Autism; Hyperactivity

Aggression, conflict

Hyperalgesia

Research tool for PET

Drugs of the future: Review. Vasopressin antagonists. 2006.

http://www.springerlink.com/content/u66x656j7q3n5t47/

Possible roles of Avprlb antagonists in veterinary use:

It can reduce aggression, conflict, stress, hyperactivity, and may promote the sexual

reproduction in all mammals, males and females (pandas, horses, sheeps, etc.) and work in the kidrearing, and the kid's cohesion for the adults.

http://www.springerlink.com/content/u66x656j7q3n5t47/

http://bmb.pharma.hr/lauc/NI/333.pdf

Combining with Sildenafil through reducing anorgasmy it may promote the natural occasions of reproduction too.

In China we can reorganize the animal husbandry, the fauna of green national parks and the planned animal births

The base of the medicine: the molecule

V1/V3 antagonist Manning- peptide:

X=D-Tyr-Phe-Val-Asn-Arg-Pro-Arg-Arg-NH2

http://endo.endojournals.org/content/138/10/4109.full.pdf

Our molecule is very simple

Each peptide labor can produce it in the EU, China or the US

The molecule derives from a free source (see attached file),

but the way it affects those who use it is our patent

Is it a hormone?

This is analogue to a hormone,

but it doesn't have hormonal effects like steroids,

because it works only in the brain, and

it doesn't have an effect on other parts of the body

Usage of the medicine

It is a fairly stable peptide,

can be kept it in ampullas, and

add it in intravenous injection

Price and value

The market value of this drug is huge, because only micrograms are needed from the drug, and it can be produced from very cheap ingredients

It is very economical: an industrial production of one microgram is 5 dollar

In comparison rats received from the concurrent complicated polycyclic SSR vaptans 10-30 mg/kg

Experimental introduction

We would like the experimental introduction of this molecule

The price of our project is between 1 - 1,5 million dollars plus the experimental cost - see attached file

SWOT analysis of Manning peptide molecule vs. vaptans in brain research: **Strengths**

Manning peptide	Vaptans
Specific to brain V1a/V3 receptors	Interfere with other receptors (V2, OT, body)
Similar to endogeneous VP	No
No side effects	Severe side effects
Easily traceable, F18	SSR149415 has been radiolabelled with tritium and used in receptor autoradiography
Should be administered rarely	Should be administered often
Get thru blood-brain barrier	No
Cheap	Expensive
Free	Patented

SWOT analysis: **Weaknesses**

Manning peptide	Vaptans
Moderately researched	Extensively researched
No	FDA approved
I.v. Administration	Oral intake

SWOT analysis: **Opportunities**

Manning peptide	Vaptans
Map brain v1b/v3 receptors with PET	No

It can be marked with the most long-term method, that is the F18, which is harmless. It can be used as a detailed research tool	You cannot make a tracer of it with F18
Radiopharmacon for PET	Oral intake
Treatment of anorgasmy May be combined with Sildenafil	No
Non-linear dose-dependency may lead to novel discovery (monotonicity, U-shaped or other dose-response)	No
Possible veterinary use	No

SWOT analysis: **Threats**

Manning peptide	Vaptans
No	Severe side effects
Remains ”only” a research tool for PET?	No. (Therapeutical use)
No	Most important factor determining specificity of non-peptide antagonists seems to be the shape of the binding pocket on the receptor

Research proposal

Please see the attached document on IND Application Draft: Clinical Study Protocol.

Thank you for your attention!