UNIVERSITI PUTRA MALAYSIA

EFFECTS OF Erythroxylum Cuneatum (Miq.) Kurz ON CELLULAR AND SYNAPTIC ADAPTATION OF CHRONIC MORPHINE-ADDICTED HUMAN NEUROBLASTOMA CELL LINE AT PROTEIN LEVEL

NOOR AZUIN BINTI SULIMAN

FPSK(P) 2017 10

EFFECTS OF *Erythroxylum Cuneatum* (Miq.) Kurz ON CELLULAR AND SYNAPTIC ADAPTATION OF CHRONIC MORPHINE-ADDICTED HUMAN NEUROBLASTOMA CELL LINE AT PROTEIN LEVEL

By

NOOR AZUIN BINTI SULIMAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

March 2017

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of **Doctor of Philosophy**

EFFECTS OF ERYTHROXYLUM CUNEATUM (MIQ.) KURZ ON CELLULAR AND SYNAPTIC ADAPTATION OF CHRONIC MORPHINE-ADDICTED HUMAN NEUROBLASTOMA CELL LINE AT PROTEIN LEVEL

By

NOOR AZUIN BINTI SULIMAN

March 2017

Chair: Mohamad Aris Bin Mohd Moklas, PhD
Faculty: Medicine and Health Sciences

Erythroxylum cuneatum (*E. cuneatum*) is a tropical flowering plant listed under Erythroxylaceae family. *E. cuneatum* is widely distributed within Southeast Asia. Uses of *E. cuneatum* in alternative medicines or remedies are limited. Indigenous traditional healer claimed that the plant was used in treating drug withdrawal. However, there is no scientific data to support the claim. Thus, the study was designed to evaluate the potential of anti-withdrawal properties of alkaloid extract of the plant on chronic morphine-addicted cell. An alkaloid extract of *E. cuneatum* (designated as ECAl) was extracted for all the tests. The human neuroblastoma cell line, SK-N-SH, was used throughout the study. The effects of ECAl on the chronic morphine-addicted cell were observed in two different groups, the co- and pre-treatments of morphine. Throughout the study, ECAl (0.1, 0.5, and 1.0 µg/mL) was compared to morphine and methadone. The receptor involved for the effects of the plant was determined using antagonists. The expressions of Cyclic adenosine 3', 5'-monophosphate (cAMP), intracellular calcium ion ($[Ca^{2+}]_i$), and α-synuclein were studied. At the beginning of the study, withdrawal markers [α-synuclein and calmodulin] were observed, followed by the receptor trafficking [Vesicle-associated membrane protein 2 (VAMP 2) and synaptotagmin 1], desensitisation or internalisation of the receptor [G protein-coupled receptor kinases (GRK) 2, β-arrestin 1/2, and clathrin], and cellular adaptation [mitogen-activated protein (MAP)/extracellular signal-regulated (ERK) kinase (MEK) 1/2, ERK 2, cAMP-

dependent protein kinase (PKA), and protein kinase C (PKC)] affected by the ECAl. Through the receptor affinity studies, ECAl bound to μ-opioid receptor, similar to methadone and morphine. Present data showed that ECAl possesses anti-withdrawal properties. ECAl was observed to enhance the receptor trafficking and cause the internalisation of the receptor. The cellular and synaptic adaptations modulated by ECAl were consistent throughout all study and parallel with the effects of the methadone. The administration of ECAl at the optimal doses was postulated to minimise the withdrawal, dependence, and tolerance against morphine-addicted cell. The alkaloid extract of the plant has a potential in opioid substitution therapy.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KESAN-KESAN TERHADAP ADAPTASI SEL DAN SINAPS OLEH *ERYTHROXYLUM CUNEATUM*

Oleh

NOOR AZUIN BINTI SULIMAN

Mac 2017

Pengerusi: Mohamad Aris Bin Mohd Moklas, PhD
Fakulti: Perubatan dan Sains Kesihatan

Erythroxylum cuneatum (*E. cuneatum*) adalah tumbuhan berbunga tropika yang disenaraikan di bawah keluarga Erythroxylaceae. *E. cuneatum* tumbuh secara meluas di Asia Tenggara. Penggunaan *E. cuneatum* sebagai ubat-ubatan atau rawatan alternatif adalah terhad. Terdapat dakwaan oleh pengamal perubatan tradisional dikalangan orang asli mengenai penggunaan tumbuhan ini dalam merawat ketagihan dadah. Walau bagaimanapun, tiada data saintifik untuk menyokong dakwaan tersebut. Oleh itu, kajian ini bertujuan untuk mengkaji kewujudan ciri-ciri anti-ketagihan dalam ekstrak alkaloid tumbuhan ke atas sel yang terawat dengan morfin secara kronik. Ekstrak alkaloid *E. cuneatum* (dinyatakan sebagai ECAl) telah diekstrak untuk semua ujian. Sel neuroblastoma manusia, SK-N-SH, telah digunakan untuk kajian ini. Kesan ECAl pada kronik morfin diperhatikan dalam dua kumpulan yang berbeza iaitu rawatan bersama dan pra-rawatan morfin. Sepanjang kajian ini, ECAl (0.1, 0.5, dan 1.0 µg/mL) dibandingkan dengan morfin dan metadon. Reseptor yang terlibat bagi kesan tumbuhan itu telah ditentukan dengan menggunakan antagonis. Ekspresi cyclic adenosine 3 ', 5'-monophosphate (cAMP), kalsium ion intrasel ($[Ca2 +]_i$), dan α-synuclein telah dikaji. Di awal kajian, protein sebagai indikasi penarikan (α-synuclein dan calmodulin) telah diperhatikan, diikuti dengan kitaran reseptor [vesicle-associated membrane protein 2 (VAMP 2) dan synaptotagmin 1], penyahpekaan atau internalisasi reseptor [G protein-coupled receptor kinases (GRK) 2, β-arrestin 1/2, dan clathrin], dan adaptasi sel [mitogen-activated protein (MAP)/extracellular signal-regulated (ERK) kinase (MEK) 1/2, ERK 2, cAMP-dependent protein kinase (PKA), dan protein kinase C (PKC)] dipengaruhi oleh ECAl. Melalui kajian terhadap afiniti reseptor, ECAl terikat untuk µ-opioid reseptor, sama seperti metadon dan morfin. Data kajian

menunjukkan bahawa ECAl mempunyai ciri-ciri anti-penyingkiran. ECAl diperhatikan meningkatkan kitaran reseptor dan menyebabkan internalisasi reseptor. Adaptasi sel dan sinaps oleh ECAl adalah konsisten dengan semua kajian dan selari dengan kesan metadon. Penggunaan ECAl pada dos optimum diandaikan dapat mengurangkan penyingkiran, kebergantungan, dan toleransi terhadap morfin. Ekstrak alkaloid tumbuhan ini berpotensi sebagai pilihan dalam terapi gentian pioid.

ACKNOWLEDGEMENTS

"In the name of Allah S.W.T, the most Benevolent and Most Merciful"

Praise to Allah for granting me grace and strength to persevere throughout my study and to overcome all the challenges that I have gone through during the project.

I would like to express my deepest gratitude to my supervisor Associate Professor Dr. Mohamad Aris Mohd Moklas for his full support, expert guidance, understanding and encouragement throughout my study and research. Without his incredible patience and timely wisdom and counsel, my thesis work would have been a frustrating and overwhelming pursuit. In addition, I express my appreciation to Dr. Che Norma Mat Taib and Professor Mohd Ilham Adenan for having served on my committee. Their thoughtful questions and comments were valued greatly.

I would also like to thank all the post-graduate students and staffs of the Department of Human Anatomy for their help throughout my study. Special thanks go to my few friends who helped and supported me during my study and writing of the thesis.

Finally, I would like to thank my parents; Suliman Bin Sukar and Zainab Binti Jidon, siblings, and close family members for their unconditional love and support during the last three years. I would not have been able to complete this thesis without their continuous love and encouragement.

APPROVAL

I certify that a Thesis Examination Committee has met on (date of viva voce) to conduct that final examination of Noor Azuin Binti Suliman on her thesis entitle "Exploration of *Erythroxylum Cuneatum* on Cellular and Synaptic Adaptation" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded with (insert the name of relevant degree).

Members of the Thesis Examination Committee were as follows:

Sharida binti Fakurazi, PhD
Associate Professor Datin
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Norshariza binti Nordin, PhD
Dr.
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Md Zuki bin Abu Bakar @ Zakaria, PhD
Professor
Institute of Bioscience
Universiti Putra Malaysia
(Internal Examiner)

David Kendall, PhD
Professor
School of Pharmacy and Biomolecular Sciences
Liverpool John Moores University
United Kingdom
(External Examiner)

ZULKARNAIN ZAIAL, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of (type of degree). The members of the Supervisory Committee were as follows:

Mohamad Aris Bin Mohd Moklas, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Che Norma Binti Mat Taib, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Mohd Ilham Adenan, PhD
Professor
Atta-ur-Rahman Institute for Natural Product Discovery
University of Technology (MARA)
(Member)

ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotation, illustrations and citations have neen duly referenced;
- this thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular witings, seminar papers, manuscripts, poster, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Reseach) Rules 2012. The thesis has undergone plagiarism detection software.

Signature:_____ Date:_____

Name and Matric No.:_____

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhere to.

Signature: _____

Name of Chairman of Supervisory Committee: Associate Professor Dr. Mohamad Aris Bin Mohd Moklas

Signature: _____

Name of Member of Supervisory Committee: Dr. Che Norma Binti Mat Taib

Signature: _____

Name of Member of Supervisory Committee: Professor Dr. Mohd Ilham Adenan

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

$[Ca^{2+}]_i$	Concentration of intracellular calcium ion
βARK 1	β-adrenergic receptor kinase 1
5-HT	5-hydroxytryptamine
AC	Adenylyl cyclase
ACh	Acethylcholine neurotransmitter
AFDX-116	11-[[2-[(diethylamino)methyl]-l-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-on
ANOVA	Analysis of variance
AP-2	Adaptor protein 2
ATCC	American Type Culture Collection
ATP	Adenosine triphosphate
APS	Ammonium persulfate
Ca^{2+}	Calcium ion
Ca^{2+}-CaM	Ca^{2+}-calmodulin
CAMKII	Ca^{2+}/calmodulin-dependent protein kinase II
cAMP	Cyclic adenosine 3', 5'-monophosphate
cGMP/PKG	Cyclic guanosine 3',5'-monophosphate / protein kinase G
CME	Clathin-mediated endocytosis
CNS	Central nervous system
CPP	Conditioned place preference
CREB	cAMP response element-binding protein

DA	Dopamine
DAG	Diacylglycerol
DAO	Diamineoxide
DMSO	Dimethyl sulfoxide
ECAl	Alkaloid extract of *Erythroxylum cuneatum*
EGR1	Early growth response 1
ELISA	Enzyme-linked immunosorbent assay
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinase
FBS	Fetal bovine serum
FRIM	Forest Research Institution of Malaysia
GDP	Guanosine diphosphate
GIRK	G protein-linked inwardly rectifying K^+ channels
GRK	G protein-coupled receptor kinases
GPCR	G protein-coupled receptor
GTP	Guanosine triphosphate
HCl	Hydrochloride acid
HRP	Horseradish peroxide
Hr(s)	Hour (s)
IBMX	Isobutylmethylxanthine
IDV	Integrated density values
IFN-γ	Interferon-γ
IH	Voltage-dependent current

IP3	Inositol triphosphate
JNK	C-Jun N-terminal kinase
K^+	Potassium
K_{ATP}	Adenosine triphosphate (ATP)-sensitive K^+
LC	Locus coeruleus
LTD	Long-term depression
LTP	Long-term potential
M	Muscarinic receptor
MAP	Mitogen-activated protein
MAPK	Mitogen-activated protein (MAP) kinase
MEM	Minimum essential medium
MEK	Mitogen-activated protein (MAP)/extracellular signal-regulated (ERK) kinase
Min (s)	Minute (s)
MRI	Mean relative intensity
MTT	Thiazolyl blue tretrazolium bromideme
NA	Noradrenaline
NADH	Nicotinamide adenine dinucleotide
NE	Norepinephrine
NMDA	N-methyl-D-aspartate receptors
NO	Nitric oxide
OST	Opioid substitution therapy
PBS	Phosphate buffer saline
PDE	Phosphodiesterase

pERK	Phosphorylated ERK1/2
PIP2	Phosphatidylinositol 4,5-bisphosphate
PKA	cAMP-dependent protein kinase
PKC	Protein kinases C
PKCε	Phosphokinase C
PLA2	Phospholipase A_2
PLC	Phospholipase C
PMT	Putrescine N-methyltransferase
PNS	Peripheral nervous system
PSD	Post-synaptic density
PVDF	Polyvinylidene difluoride
RA	Retinoid acid
RIPA	Radioimmunoprecipitation assay
RNA	Ribonucleic acid
RNApol	Ribonucleic acid polymerase
RSK	Ribosomol S6 Kinase
SAPK	Stress-activated protein kinases
SDS	Sodium dodecyl sulfate
SFK	Src family kinase
SNARE	Soluble N-ethylmaleimide-sensitive factor activating protein receptor
t-SNARE	Target soluble N-ethylmaleimide-sensitive factor activating protein receptor
TBST	Tris-buffered saline and tween 20

TEMED	Tetramethylethylenediamine
TR-I	Tropinone reductase I
TR-II	Tropinone reductase II
UK	United Kingdom
UPM	Universiti Putra Malaysia
USA	United State of America
v-SNARE	Vesicular soluble N-ethylmaleimide-sensitive factor activating protein receptor
VAMP 2	Vesicle-associated membrane protein 2
VDCC	Voltage-gated Ca^{2+} channel
VTA	Ventral tegmental area

CHAPTER 1

INTRODUCTION

1.1 Background of study

Three classes of medication that responsible for misuse liability are prescription opioids, stimulants, and the central nervous system (CNS) depressants. There are the number of factors that contribute to such phenomenon which includes great distribution of medications, aggressive marketing by pharmaceutical companies, and easy accessibility to public users. These contributing factors escalate the number of non-medical usage of opioid analgesic and overdose deaths (Mack, 2013).

In 2013, more than 11 million people mistreated with heroin or prescription pain reliever were recorded ("SAMHSA Releases Behavioral Health, United States, 2012", 2013). There is a long list of adverse effects of the opioid abuse. One of the major problems of opioid abuse is the chronic pain experienced by more than 62% of opioid substitution therapy (OST) patients (Voon et al., 2015). Meanwhile, 30.7% of general population grieved the pain (Johannes et al., 2010). The chronic pain is observed from the exhibition of opioid-induced hyperalgesia and super-sensitivity to pain (Williams et al., 2001).

Repeated intake of opioids causes the inhibition of production of endogenous opioids such as endorphins and encephalins. The cellular adaptation is responsible for the withdrawal, tolerance, and dependence signs. These addictive symptoms in future will trigger the drug addicts to increase their uptake of the drug to obtain desired effects. This subsequential event will lead to overdose, a new problem of drug usage (Williams et al., 2001).

Opioids are effective for acute severe pain following trauma, extensive burns, or surgery. They also are used for painful terminal diseases such as cancer (Pasternak, 2011). Edlund et al. (2007) claimed that the rare addiction incident occurred when opioid analgesics are used appropriately. At the same time, Ballantyne and LaForge (2007) suggested that chronic opioid on chronic pain patient has increased the addiction and opioid abuse. Thus, it is consistent with Kalso et al. (2004) proclaimed the effective analgesia in chronic pain patient treated with the acute opioid. To what extent is a prescription of painkillers to create an epidemic abuse? The answer is not simple (Fields, 2011). Fields (2011)

suggested that more than 70% of the opioid abusers got the drug unlawfully while less than 20% got the drugs through a prescription from a doctor. Some users overdose or wind up dead from respiratory depression (Edlund et al., 2007).

1.2 Problem statement

Opioids, such as morphine, heroin, and oxycodone, act as an agonist of the μ-opioid receptor to produce analgesia effect. Though, drugs activating μ-opioid receptor are most commonly abused (Koob and Le Moal, 2005). Opioid addiction becomes an epidemic problems. One death in every 19 minutes was recorded in the United States only (Centers for Disease Control and Prevention (CDC), 2012). Morphine, a recreational drug, is a pain-relieving medication prescribed among practitioners. It causes addiction and even fatal withdrawal symptoms, including stroke, heart attack, and severe pains ("Morphine Addiction and Treatment- Future of Palm Beach", 2016).

There are numbers of therapies or commercialised drugs that are used to treat opioid addiction, withdrawal, tolerance, or overdoses such as buprenorphine, methadone, and clonidine (Doyon et al., 2004). However, these drugs are classified as opioid and widely known to cause abuse (Bailey et al., 2009). Prescribed opioid addiction or morphine addiction patients in the US are enrolled in methadone maintenance treatments programs (Rosenblum et al., 2007).

Methadone is an opioid agonist that is effective for treating severe pain. It has potential advantages against another opioid including low cost, high bioavailability, long half-life, and lack of active metabolites. According to the National Institutes of Health, the government of United States spent over $180 billion for illicit drug abuse just in 2008. The costs include the medical expenses and unlawful activity, social welfare, secondary medical issues, and efficiency losses. The misuse of methadone and opioid contributes to noticeable economic burden to civilisation (Scavone et al., 2013). Furthermore, methadone substitution as a treatment for opioid addiction has been criticised widely. It is claimed that the methadone is not effective to restraint addiction (Bennett, 2011).

The focus of the management is to confront the negative impact of the abuse on health and mortality while preserving the role of the opioid in managing pain. The use of alternative medicines is one of the options to deal with opioid misusage. The local Malaysian folks claim the use of Chinta Mula on treating morphine craving. Chinta Mula or scientifically known as *Erythroxylum*

cuneatum (EC) can be found in Southeast Asia, especially in Malaysia, Philippine, and Indonesia (Chung, 2006). EC belongs to the family of Erythroxylaceae, *Erythroxylum spp.* and contains cocaine as one of its psychoactive alkaloid that proclaimed to influence the CNS (Plowman and Rivier, 1983).

1.3 Significance of the study

The output from this study will provide a new approach in regards to managing the opioid misuse. Instead of using a drug to treat misuse of the drug, alternative medicines such as plant will be a better approach. As compared to commercialised drugs, alternative medicines are cheaper and comparatively safer.

1.4 Hypothesis

Following the problem statements, the hypothesis of the study is that *Erythroxylum cuneatum* (EC) is mimicking the effects of methadone against the induction of morphine. EC is hypothesised to express anti-addiction properties; anti-dependence, anti-tolerance, and anti-withdrawal, against chronic morphine. EC is expected to minimise the addiction symptoms on the morphine-treated cell line observed by increasing fusion machinery at the pre-synaptic terminal internalising the involved receptor and influencing the cellular adaptation processes.

1.5 Objectives of the study

General Objective

- To observe the anti-withdrawal properties of alkaloid extract of EC (designated as ECAl) by comparing to methadone in morphine-induced addicted cell line.

Specific Objectives

1. To determine the ideal dosage of ECAl on treating the morphine-treated cell on different time duration.

2. To predict the involvement of receptor on withdrawal properties of ECAl.
3. To examine the role of ECAl in the fusion machinery at the pre-synaptic terminal against chronic morphine.
4. To predict the effects of ECAl on desensitisation/internalisation of receptor on the morphine-treated cell line.
5. To study the cellular adaptation induced by the prolonged morphine and counteracting of ECAl.

REFERENCES

Abadinsky, H. (2010). *Drug use and abuse: A comprehensive introduction*. Nelson Education.

Abdul Salam, R. (2010). *Protective effect of Erythroxylum cuneatum and Mitragyna speciosa leaf extract on RAW 264.7 and MCF-7*. (Published Bachelor dissertation). Universiti Teknologi MARA (UiTM).

Adams, J. P., & Sweatt, J. D. (2002). Molecular psychology: roles for the ERK MAP kinase cascade in memory. *Annual Review of Pharmacology and Toxicology*, *42*(1): 135-163.

Aghajanian, G. K., & Wang, Y. Y. (1986). Pertussis toxin blocks the outward currents evoked by opiate and α 2-agonists in locus coeruleus neurons. *Brain Research*, *371*(2): 390-394.

Ahmed, S., Anuntiyo, J., Malemud, C. J., & Haqqi, T. M. (2005). Biological basis for the use of botanicals in osteoarthritis and rheumatoid arthritis: a review. *Evidence-Based Complementary and Alternative Medicine*, *2*(3): 301-308.

Al-Hasani, R., & Bruchas, M. R. (2011). Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Journal of the American Society of Anesthesiologists*, *115*(6): 1363-1381.

Allen, T. G., & Burnstock, G. (1990). M1 and M2 muscarinic receptors mediate excitation and inhibition of guinea-pig intracardiac neurones in culture. *Journal of Physiology*, 422(1): 463-480.

Almela, P., Cerezo, M., Milanés, M. V., & Laorden, M. L. (2006). Role of PKC in regulation of Fos and TH expression after naloxone induced morphine withdrawal in the heart. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *372*(5): 374-382.

Almela, P., Milanés, M. V., & Laorden, M. L. (2007). Activation of the ERK signalling pathway contributes to the adaptive changes in rat hearts during naloxone-induced morphine withdrawal. *British Journal of Pharmacology*, *151*(6): 787-797.

American Academy of Pain Medicine (AAPM), American Pain Society (APS), American Society of Addiction Medicine (ASAM), 2001. Definitions related to the use of opioids for the treatment of pain. Retrieved from http://www.painmed.org/productpub/statements/pdfs/definition.pdf.

Amoroso, S., Schmid-Antomarchi, H., Fosset, M., & Lazdunski, M. (1990). Glucose, sulfonylureas, and neurotransmitter release: role of ATP-sensitive K+ channels. *Science*, *247*(4944): 852-854.

Anand, K. J., Willson, D. F., Berger, J., Harrison, R., Meert, K. L., Zimmerman, J., … & Nicholson, C. (2010). Tolerance and withdrawal from prolonged opioid use in critically ill children. *Pediatrics*, *125*(5): e1208-e1225.

Andrisani, O. M. (1998). CREB-mediated transcriptional control. *Critical Reviews in Eukaryotic Gene Expression, 9*(1): 19-32.

Ansari, M. A., Wagan, M. A., & Shaikh, R. A. (2001). Role of clonidine in acute opioid Abstinence syndrome. *Pakistan Journal of Medical Sciences*, *17*(3): 163-168.

Asensio, V. J., Miralles, A., & García-Sevilla, J. A. (2006). Stimulation of mitogen-activated protein kinase kinases (MEK1/2) by μ-, δ-and κ-opioid receptor agonists in the rat brain: Regulation by chronic morphine and opioid withdrawal. *European Journal of Pharmacology*, *539*(1): 49-56.

Attramadal, H., Arriza, J. L., Aoki, C., Dawson, T. M., Codina, J., Kwatra, M. M., ... & Lefkowitz, R. J. (1992). Beta-arrestin2, a novel member of the arrestin/beta-arrestin gene family. *Journal of Biological Chemistry*, *267*(25): 17882-17890.

Audet, N., Paquin-Gobeil, M., Landry-Paquet, O., Schiller, P. W., & Piñeyro, G. (2005). Internalization and Src activity regulate the time course of ERK activation by delta opioid receptor ligands. *Journal of Biological Chemistry*, 280(9): 7808-7816.

Augustin, I., Korte, S., Rickmann, M., Kretzschmar, H. A., Südhof, T. C., Herms, J. W., & Brose, N. (2001). The cerebellum-specific Munc13 isoform Munc13-3 regulates cerebellar synaptic transmission and motor learning in mice. *Journal of Neuroscience*, *21*(1): 10-17.

Bailey, C. P., & Connor, M. (2005). Opioids: cellular mechanisms of tolerance and physical dependence. *Current Opinion in Pharmacology*, *5*(1): 60-68.

Bailey, J. E., Campagna, E., Dart, R. C., & RADARS System Poison Center Investigators. (2009). The underrecognized toll of prescription opioid abuse on young children. *Annals of Emergency Medicine*, *53*(4): 419-424.

Ballantyne, J. C., & LaForge, S. K. (2007). Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*, *129*(3), 235-255.

Baptista, M. J., O'Farrell, C., Daya, S., Ahmad, R., Miller, D. W., Hardy, J., ... & Cookson, M. R. (2003). Co-ordinate transcriptional regulation of dopamine synthesis genes by α-synuclein in human neuroblastoma cell lines. *Journal of Neurochemistry*, *85*(4): 957-968.

Barnes, P. J. (2004). Distribution of receptor targets in the lung. *Proceedings of the American Thoracic Society*, 1(4): 345-351.

Bartko, S. J., Winters, B. D., Saksida, L. M., & Bussey, T. J. (2014). Different roles for M1 and M2 receptors within perirhinal cortex in object recognition and discrimination. *Neurobiology of Learning and Memory*, *110*: 16-26

Bedford, F. K. (2009). Receptor Trafficking. In *Encyclopedia of Neuroscience* (pp. 3385-3389). Springer Berlin Heidelberg.

Beker, F., Weber, M., Fink, R. H., & Adams, D. J. (2003). Muscarinic and nicotinic ACh receptor activation differentially mobilize Ca2+ in rat intracardiac ganglion neurons. *Journal of Neurophysiology*, *90*(3): 1956-1964.

Belcheva, M. M., Vogel, Z., Ignatova, E., Avidor-Reiss, T., Zippel, R., Levy, R., ... & Coscia, C. J. (1998). Opioid modulation of extracellular signal-regulated protein kinase activity is Ras-dependent and involves Gβγ subunits. *Journal of Neurochemistry*, *70*(2): 635-645.

Belcheva, M. M., Clark, A. L., Haas, P. D., Serna, J. S., Hahn, J. W., Kiss, A., & Coscia, C. J. (2005). μ and κ opioid receptors activate ERK/MAPK via different protein kinase C isoforms and secondary messengers in astrocytes. *Journal of Biological Chemistry*, *280*(30): 27662-27669.

Bencharit, S., Morton, C. L., Xue, Y., Potter, P. M., & Redinbo, M. R. (2003). Structural basis of heroin and cocaine metabolism by a promiscuous human drug-processing enzyme. *Nature Structural and Molecular Biology*, *10*(5): 349-356.

Bennett, C. (2011). Methadone maintenance treatment: disciplining the 'addict'. *Health and History*, *13*(2): 130-157.

Berens, R. J., Meyer, M. T., Mikhailov, T. A., Colpaert, K. D., Czarnecki, M. L., Ghanayem, N. S., ... & Weisman, S. J. (2006). A prospective evaluation of opioid weaning in opioid-dependent pediatric critical care patients. *Anesthesia and Analgesia*, *102*(4): 1045-1050.

Berger, A. C., & Whistler, J. L. (2010). How to design an opioid drug that causes reduced tolerance and dependence. *Annals of Neurology*, *67*(5): 559-569.

Bernhoft, A. (2010). A brief review on bioactive compounds in plants. *Proceedings from a symposium held at The Norwegian Academy of Science and Letters*. Pp. 11–13. Oslo, Norway

Bernstein, M. A., & Welch, S. P. (1998). μ-Opioid receptor down-regulation and cAMP-dependent protein kinase phosphorylation in a mouse model of chronic morphine tolerance. *Molecular Brain Research*, *55*(2): 237-242.

Berridge, M. J., Bootman, M. D., & Lipp, P. (1998). Calcium-a life and death signal. *Nature*, *395*(6703): 645-648.

Beuerle, T., Benford, D., Brimer, L., Cottrill, B., Doerge, D., Dusemund, B., … & Mulder, P. P. J. (2013). Scientific opinion on tropane alkaloids in food and feed. *European Food Safety Authority Journal*, *11*(10): 1-113.

Bhargava, H. N. (1994). Diversity of agents that modify opioid tolerance, physical dependence, abstinence syndrome, and self-administrative behavior. *Pharmacological Reviews*, *46*(3): 293-324.

Biała, G., & Kruk, M. (2009). Influence of bupropion and calcium channel antagonists on the nicotine-induced memory-related response of mice in the elevated plus maze in mice. *Pharmacological Reports*, *61*(2): 236-244.

Bohn, L. M., Gainetdinov, R. R., Lin, F. T., Lefkowitz, R. J., & Caron, M. G. (2000). μ-opioid receptor desensitization by β-arrestin-2 determines morphine tolerance but not dependence. *Nature*, *408*(6813): 720-723.

Bollmann, J. H., Sakmann, B., & Borst, J. G. G. (2000). Calcium sensitivity of glutamate release in a calyx-type terminal. *Science*, *289*(5481): 953-957.

Bongianni, F., Carla, V., Moroni, F., & Pellegrini-Giampietro, D. E. (1986). Calcium channel inhibitors suppress the morphine-withdrawal syndrome in rats. *British Journal of Pharmacology*, *88*(3): 561-567.

Bonifacino, J. S., & Glick, B. S. (2004). The mechanisms of vesicle budding and fusion. *Cell*, *116*(2): 153-166.

Boulton, T. G., Nye, S. H., Robbins, D. J., Ip, N. Y., Radzlejewska, E., Morgenbesser, S. D., ... & Yancopoulos, G. D. (1991). ERKs: a family of protein-serine/threonine kinases that are activated and tyrosine phosphorylated in response to insulin and NGF. *Cell*, *65*(4): 663-675.

Boudinot, E., Yamada, M., Wess, J., Champagnat, J., & Foutz, A. S. (2004). Ventilatory pattern and chemosensitivity in M 1 and M 3 muscarinic receptor knockout mice. *Respiratory Physiology and Neurobiology*, *139*(3): 237-245.

Brose, N., Petrenko, A. G., Sudhof, T. C., & Jahn, R. (1992). Synaptotagmin: a calcium sensor on the synaptic vesicle surface. *Science*, *256*(5059): 1021-1025.

Breivogel, C. S., Selley, D. E., & Childers, S. R. (1997). Acute and chronic effects of opioids on δ and μ receptor activation of G proteins in NG108-15 and SK-N-SH cell membranes. *Journal of Neurochemistry*, *68*(4): 1462-1472.

Brown, M. S., Anderson, R. G., & Goldstein, J. L. (1983). Recycling receptors: the round-trip itinerary of migrant membrane proteins. *Cell*, *32*(3): 663-667.

Brunet, A., Roux, D., Lenormand, P., Dowd, S., Keyse, S., & Pouysségur, J. (1999). Nuclear translocation of p42/p44 mitogen-activated protein kinase is required for growth factor-induced gene expression and cell cycle entry. *The European Molecular Biology Organiszation Journal*, *18*(3): 664-674.

Bu, Q., Yang, Y., Yan, G., Hu, Z., Hu, C., Duan, J., ... & Deng, Y. (2012). Proteomic analysis of the nucleus accumbens in rhesus monkeys of morphine dependence and withdrawal intervention. *Journal of Proteomics*, *75*(4): 1330-1342.

Burgdorf, J., Knutson, B., Panksepp, J., & Shippenberg, T. S. (2001). Evaluation of rat ultrasonic vocalizations as predictors of the conditioned aversive effects of drugs. *Psychopharmacology*, *155*(1): 35-42.

Burgoyne, R. D., & Morgan, A. (2003). Secretory granule exocytosis. *Physiological Reviews*, *83*(2): 581-632.

Busquets, X., Escriba, P. V., Sastre, M., & García-Sevilla, J. A. (1995). Loss of protein kinase C-αβ in brain of heroin addicts and morphine-dependent rats. *Journal of Neurochemistry*, *64*(1): 247-252.

Camps, P., & Munoz-Torrero, D. (2002). Cholinergic drugs in pharmacotherapy of Alzheimer's disease. *Mini Reviews in Medicinal Chemistry*, *2*(1): 11-25.

Cao, J. L., He, J. H., Ding, H. L., & Zeng, Y. M. (2005). Activation of the spinal ERK signaling pathway contributes naloxone-precipitated withdrawal in morphine-dependent rats. *Pain*, *118*(3): 336-349.

Cao, J. L., Liu, H. L., Wang, J. K., & Zeng, Y. M. (2006). Cross talk between nitric oxide and ERK1/2 signaling pathway in the spinal cord mediates naloxone-precipitated withdrawal in morphine-dependent rats. *Neuropharmacology*, *51*(2): 315-326.

Capeyrou, R., Riond, J., Corbani, M., Lepage, J. F., Bertin, B., & Emorine, L. J. (1997). Agonist-induced signaling and trafficking of the μ-opioid receptor: role of serine and threonine residues in the third cytoplasmic loop and C-

terminal domain. *Federation of European Biochemical Societies (FEBS) Letters*, *415*(2): 200-205.

Carrigan, K. A., & Dykstra, L. A. (2007). Behavioral effects of morphine and cocaine in M1 muscarinic acetylcholine receptor-deficient mice. *Psychopharmacology*, *191*(4): 985-993.

Carroll, F. I., Howell, L. L., & Kuhar, M. J. (1999). Pharmacotherapies for treatment of cocaine abuse: preclinical aspects. *Journal of Medicinal Chemistry*, *42*(15): 2721-2736.

Centers for Disease Control and Prevention (CDC. (2012). CDC grand rounds: prescription drug overdoses-a US epidemic. *MMWR. Morbidity and Mortality Weekly Report*, *61*(1): 10.

Cerezo, M., Milanés, M. V., & Laorden, M. L. (2005). Alterations in protein kinase A and different protein kinase C isoforms in the heart during morphine withdrawal. *European Journal of Pharmacology*, *522*(1): 9-19.

Chahl, L. (1996). Experimental and clinical pharmacology: Opioids - mechanisms of action. *Australian Prescriber*, *19*(3): 63-65.

Chakrabarti, S., Law, P. Y., & Loh, H. H. (1998). Distinct differences between morphine- and [$_{D}$-Ala^{2}, *N*-MePhe^{4}, Gly-ol^{5}]-enkephalin-μ-opioid receptor complexes demonstrated by cyclic AMP-dependent protein kinase phosphorylation. *Journal of Neurochemistry*, *71*(1): 231-239.

Chang, P. A., Chen, R., & Wu, Y. J. (2005). Reduction of neuropathy target esterase does not affect neuronal differentiation, but moderate expression induces neuronal differentiation in human neuroblastoma (SK-N-SH) cell line. *Molecular Brain Research*, *141*(1): 30-38.

Chao, J., & Nestler, E. J. (2004). Molecular neurobiology of drug addiction. *Annual Review of Medicine*, *55*: 113-132.

Chen, K. W., Berger, C. C., Forde, D. P., D'Adamo, C., Weintraub, E., & Gandhi, D. (2011). Benzodiazepine use and misuse among patients in a methadone program. *BioMed Central Psychiatry*, *11*(1): 1.

Chen, C. Y., Dion, S. B., Kim, C. M., & Benovic, J. L. (1993). Beta-adrenergic receptor kinase. Agonist-dependent receptor binding promotes kinase activation. *Journal of Biological Chemistry*, *268*(11): 7825-7831.

Chen, Y., Jiang, Y., Yue, W., Zhou, Y., Lu, L., & Ma, L. (2008b). Chronic, but not acute morphine treatment, up-regulates α-Ca2+/calmodulin dependent

protein kinase II gene expression in rat brain. *Neurochemical Research*, *33*(10): 2092-2098.

Chen, K. C., Kao, P. H., Lin, S. R., & Chang, L. Sen. (2008). p38 MAPK activation and mitochondrial depolarization mediate the cytotoxicity of Taiwan cobra phospholipase A2 on human neuroblastoma SK-N-SH cells. *Toxicology Letters*, *180* (1): 53–58.

Chen, Y., & Yu, L. (1994). Differential regulation by cAMP-dependent protein kinase and protein kinase C of the mu opioid receptor coupling to a G protein-activated K+ channel. *Journal of Biological Chemistry*, *269*(11): 7839-7842.

Childers, S. R., Creese, I., Snowman, A. M., & Snyder, S. H. (1979). Opiate receptor binding affected differentially by opiates and opioid peptides. *European Journal of Pharmacology*, *55*(1): 11-18.

Chou, R., Cruciani, R. A., Fiellin, D. A., Compton, P., Farrar, J. T., Haigney, M. C., … & Zeltzer, L. (2014). Methadone safety: a clinical practice guideline from the American Pain Society and college on problems of drug dependence, in collaboration with the Heart Rhythm Society. *Journal of Pain*, *15*(4): 321-337.

Christie, M. J. (2008). Cellular neuroadaptations to chronic opioids: tolerance, withdrawal and addiction. *British Journal of Pharmacology*, *154*(2): 384-396.

"CHRM1 Cholinergic Receptor Muscarinic 1 [Homo Sapiens (Human)] - Gene - NCBI". *Ncbi.nlm.nih.gov*. N.p., 2017. Web. 10 Apr. 2017.

Chu, P., Murray, S., Lissin, D. & von Zastrow, M. (1997). δ and κ Opioid receptors are differentially regulated by dynamin-dependent endocytosis when activated by the same alkaloid agonist. *Journal of Biological Chemistry*, *272*(43): 27124-27130.

Chu, J., Zheng, H., Zhang, Y., Loh, H. H., & Law, P. Y. (2010). Agonist-dependent μ-opioid receptor signaling can lead to heterologous desensitization. *Cellular Signalling*, *22*(4): 684-696.

Chung, R. C. K. (2006). The Angiosperm Flora of Singapore: Erythroxylaceae. NUS Press.

Clayton, D. F., & George, J. M. (1999). Synucleins in synaptic plasticity and neurodegenerative disorders. *Journal of Neuroscience Research*, *58*(1): 120-129.

Cobb, M. H., & Goldsmith, E. J. (1995). How MAP kinases are regulated. *Journal of Biological Chemistry*, *270*(25): 14843-14846.

Community Epidemiology Working Group, National Institute on Drug Abuse. Epidemiological trends in drug abuse; Proceedings of the Community Epidemiology Working Group, Vol 1;June 2000.

Connor, M., & Christie, M. J. (1999). Opioid receptor signalling mechanisms.*Clinical and Experimental Pharmacology and Physiology*, *26*(7): 493-499.

Connor, M., & Henderson, G. (1996). δ-and μ-opioid receptor mobilization of intracellular calcium in SH-SY5Y human neuroblastoma cells. *British Journal of Pharmacology*, *117*(2): 333-340.

Connor, M., Osborne, P. B., & Christie, M. J. (2004). μ-Opioid receptor desensitization: Is morphine different? *British Journal of Pharmacology*, *143*(6): 685-696.

Contet, C., Kieffer, B. L., & Befort, K. (2004). Mu opioid receptor: a gateway to drug addiction. *Current Opinion in Neurobiology*, *14*(3): 370-378.

Convertino, M., Samoshkin, A., Gauthier, J., Gold, M. S., Maixner, W., Dokholyan, N. V., & Diatchenko, L. (2014). μ-Opioid receptor 6-transmembrane isoform: A potential therapeutic target for new effective opioids. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 62: 61-67.

Corey, S., Krapivinsky, G., Krapivinsky, L., & Clapham, D. E. (1998). Number and stoichiometry of subunits in the native atrial G-protein-gated K+ channel, IKACh. *Journal of Biological Chemistry*, *273*(9): 5271-5278.

Cowan, K. J., & Storey, K. B. (2003). Mitogen-activated protein kinases: new signaling pathways functioning in cellular responses to environmental stress. *Journal of Experimental Biology*, *206*(7): 1107-1115.

Crowley, T. J., Hydinger, M., Stynes, A. J., & Feiger, A. (1975). Monkey motor stimulation and altered social behavior during chronic methadone administration. *Psychopharmacologia*, *43*(2): 135-144.

Cruz, H. G., Berton, F., Sollini, M., Blanchet, C., Pravetoni, M., Wickman, K., & Lüscher, C. (2008). Absence and rescue of morphine withdrawal in GIRK/Kir3 knock-out mice. *The Journal of Neuroscience*, *28*(15): 4069-4077.

Cseke, L. J., Kirakosyan, A., Kaufman, P. B., Warber, S., Duke, J. A., & Brielmann, H. L. (2006). *Natural Products from Plants*. CRC press.

D'Arcy, Y. M. (2011). *Compact Clinical Guide to Chronic Pain Management: An Evidence-based Approach for Nurses*. Springer Publishing Company.

Dawson, G., Dawson, S. A., & Goswami, R. (1997). Chronic exposure to κ-opioids enhances the susceptibility of immortalized neurons (F-11κ7) to apoptosis-inducing drugs by a mechanism that may involve ceramide. *Journal of Neurochemistry*, *68*(6): 2363-2370.

De Weille, J. R., & Lazdunski, M. (1990). Regulation of the ATP-sensitive potassium channel. *Ion Channels*, *2*: 205-222.

De Vries, T. J., & Shippenberg, T. S. (2002). Neural systems underlying opiate addiction. *Journal of Neuroscience*, *22*(9): 3321-3325.

Deak, M., Clifton, A. D., Lucocq, J. M., & Alessi, D. R. (1998). Mitogen-and stress-activated protein kinase-1 (MSK1) is directly activated by MAPK and SAPK2/p38, and may mediate activation of CREB. *The European Molecular Biology Organization Journal*, *17*(15): 4426-4441.

DeLorenzo, R. J. (1982, May). Calmodulin in neurotransmitter release and synaptic function. *In Federation Proceedings* (Vol. 41, No. 7, pp. 2265-2272).

Dennis, B. B., Samaan, M. C., Bawor, M., Paul, J., Plater, C., Pare, G., …, & Samaan, Z. (2014). Evaluation of clinical and inflammatory profile in opioid addiction patients with comorbid pain: results from a multicenter investigation. *Neuropsychiatric Disease and Treatment*, *10*: 2239.

Dhanasekaran, N., Heasley, L. E., & Johnson, G. L. (1995). G protein-coupled receptor systems involved in cell growth and oncogenesis. *Endocrine Reviews*, *16*(3): 259-270.

Dhingra, L., Perlman, D. C., Masson, C., Chen, J., McKnight, C., Jordan, A. E., … & Cheatle, M. D. (2015). Longitudinal analysis of pain and illicit drug use behaviors in outpatients on methadone maintenance. *Drug and Alcohol Dependence*, *149*: 285-289.

Diao, J., Burré, J., Vivona, S., Cipriano, D. J., Sharma, M., Kyoung, M., ... & Brunger, A. T. (2013). Native α-synuclein induces clustering of synaptic-vesicle mimics via binding to phospholipids and synaptobrevin-2/VAMP2. *Elife*, *2*: e00592.

Dopico, A. M., Lemos, J. R., & Treistman, S. N. (1996). Ethanol increases the activity of large conductance, Ca (2+)-activated K+ channels in isolated neurohypophysial terminals. *Molecular Pharmacology*, *49*(1): 40-48.

Doyon S. Opiods. In: Tintinalli JE, Kelen GD, Stapczynski JS, Ma OJ, Cline DM, eds. *Emergency Medicine: A Comprehensive Study Guide*. 6th ed. New York, NY: McGraw-Hill; 2004: chap 167.

Dubrovina, N. I., & Ilyutchenok, R. Y. (1996). Dopamine and opioid regulation of the memory retrieval recovery in mice. *Behavioural Brain Research*, *79*(1): 23-29.

Duffy, G. (2008). First Coca Find in Brazil Amazon. *BBC News*.

Duman, R. S. (1998). Novel therapeutic approaches beyond the serotonin receptor. *Biological Psychiatry*, *44*(5): 324-335.

Dunn, K. E., Finan, P. H., Tompkins, D. A., Fingerhood, M., & Strain, E. C. (2015). Characterizing pain and associated coping strategies in methadone and buprenorphine maintained patients. *Drug and Alcohol Dependence*, *157*: 143-149.

DuPen, A., Shen, D., & Ersek, M. (2007). Mechanisms of opioid-induced tolerance and hyperalgesia. *Pain Management Nursing*, *8*(3): 113-121.

Edlund, M. J., Steffick, D., Hudson, T., Harris, K. M., & Sullivan, M. (2007). Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain*, *129*(3): 355-362.

Eglen, R. M. (2006). Muscarinic receptor subtypes in neuronal and non-neuronal cholinergic function. *Autonomic and Autacoid Pharmacology*, 26(3): 219-233.

Ehleringer, J. R., Casale, J., Cooper, D. A., & Lott, M. J. (2001). Sourcing drugs with stable isotopes. University of Utah Institutional Repository

Eisenstein, T. K., & Hilburger, M. E. (1998). Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations. *Journal of Neuroimmunology*, *83*(1): 36-44.

El-Imam, Y., Evans, W. C., & Grout, R. J. (1988). Alkaloids of *Erythroxylum cuneatum, E. Ecarinatum* and *E. Australe*. *Phytochemistry*, *27*(7): 2181–2184.

Erika, M. D. O., Lima, L. S., David, J. M., do Vale, A. E., Lopes, L. M., & David, J. P. (2013). A new tropane alkaloid and other constituents of *Erythroxylum rimosum* (Erythroxylaceae). *Phytochemistry Letters*, *6*(2): 232-235.

Eriksson, P. S., Carlsson, B., Isaksson, O. G., Hansson, E., & Rönnbäck, L. (1992). Altered amounts of G-protein mRNA and cAMP accumulation after long-term opioid receptor stimulation of neurons in primary culture from the rat cerebral cortex. *Molecular Brain Research*, *14*(4): 317-325.

Esmaeili-Mahani, S., Shimokawa, N., Javan, M., Maghsoudi, N., Motamedi, F., Koibuchi, N., & Ahmadiani, A. (2008). Low-dose morphine induces hyperalgesia through activation of Gαs, protein kinase C, and l-type Ca2+ channels in rats. *Journal of Neuroscience Research*, *86*(2): 471-479.

Evans, R. M., & Zamponi, G. W. (2006). Presynaptic Ca 2+ channels–integration centers for neuronal signaling pathways. *Trends in Neurosciences*, *29*(11): 617-624.

Fan, G. H., Wang, L. Z., Qiu, H. C., Ma, L., & Pei, G. (1999). Inhibition of calcium/calmodulin-dependent protein kinase II in rat hippocampus attenuates morphine tolerance and dependence. *Molecular Pharmacology*, *56*(1): 39-45.

Ferguson, R. E., Carroll, H. P., Harris, A., Maher, E. R., Selby, P. J., & Banks, R. E. (2005). Housekeeping proteins: a preliminary study illustrating some limitations as useful references in protein expression studies. *Proteomics*, *5*(2): 566-571.

Ferguson, S. S. (2001). Evolving concepts in G protein-coupled receptor endocytosis: the role in receptor desensitization and signaling. *Pharmacological Reviews*, *53*(1): 1-24.

Ferguson, S. S., Downey III, W. E., Colapietro, A. M., & Barak, L. S. (1996). Role of beta-arrestin in mediating agonist-promoted G protein-coupled receptor internalization. *Science*, *271*(5247): 363.

Ferguson, S. S., Ménard, L., Barak, L. S., Koch, W. J., Colapietro, A. M., & Caron, M. G. (1995). Role of phosphorylation in agonist-promoted β2-adrenergic receptor sequestration rescue of a sequestration-defective mutant receptor by βARK1. *Journal of Biological Chemistry*, *270*(42): 24782-24789.

Ferrer-Alcón, M., J García-Fuster, M., La Harpe, R., & García-Sevilla, J. A. (2004). Long-term regulation of signalling components of adenylyl cyclase and mitogen-activated protein kinase in the pre-frontal cortex of human opiate addicts. *Journal of Neurochemistry*, *90*(1): 220-230.

Fields, A., Gafni, M., Oron, Y., & Sarne, Y. (1995). Multiple effects of opiates on intracellular calcium level and on calcium uptake in three neuronal cell lines. *Brain Research*, *687*(1): 94-102.

Fields, H. L. (2011). The doctor's dilemma: opiate analgesics and chronic pain. *Neuron*, *69*(4): 591-594.

Fine, P. G., & Portenoy, R. K. (2004). The endogenous opioid system. *A clinical guide to opioid analgesia. McGraw Hill, New York*.

Finn, A. K., & Whistler, J. L. (2001). Endocytosis of the mu opioid receptor reduces tolerance and a cellular hallmark of opiate withdrawal. *Neuron*, *32*(5): 829-839.

Fisher, A. (2000). Therapeutic strategies in Alzheimer's disease. M1 muscarinic agonists. *Japanese Journal of Pharmacology*, *84*(2): 101-112.

Fleming, L. M., Ponjee, G., & Childers, S. R. (1992). Inhibition of protein phosphorylation by opioid-inhibited adenylyl cyclase in rat brain membranes. *Journal of Pharmacology and Experimental Therapeutics*, *260*(3): 1416-1424.

Fundytus, M. E., & Coderre, T. J. (1996). Chronic inhibition of intracellular Ca 2+ release or protein kinase C activation significantly reduces the development of morphine dependence. *European Journal of Pharmacology*, *300*(3): 173-181.

Galeotti, N., Quattrone, A., Vivoli, E., Bartolini, A., & Ghelardini, C. (2008). Type 1 and type 3 ryanodine receptors are selectively involved in muscarinic antinociception in mice: an antisense study. *Neuroscience*, *153*(3): 814-822.

Gallwitz, D., & Jahn, R. (2003). The riddle of the Sec1/Munc-18 proteins–new twists added to their interactions with SNAREs. *Trends in Biochemical Sciences*, *28*(3): 113-116.

García-Sevilla, J. A., Ventayol, P., Busquets, X., La Harpe, R., Walzer, C., & Guimón, J. (1997). Regulation of immunolabelled μ-opioid receptors and protein kinase C-α and ζ isoforms in the frontal cortex of human opiate addicts. *Neuroscience Letters*, *226*(1): 29-32.

Gavin, A. C., & Nebreda, A. R. (1999). A MAP kinase docking site is required for phosphorylation and activation of p90 rsk/MAPKAP kinase-1. *Current Biology*, *9*(5): 281-286.

Gelber, E. I., Kroeze, W. K., Roth, B. L., Gray, J. A., Sinar, C. A., Hyde, E. G., ... & Benovic, J. (1999). Structure and function of the third intracellular loop of the 5-hydroxytryptamine$_{2A}$ receptor: The third intracellular loop is α-helical and binds purified arrestins. *Journal of Neurochemistry*, *72*(5): 2206-2214.

Gold, S. J., Han, M. H., Herman, A. E., Ni, Y. G., Pudiak, C. M., Aghajanian, G. K., ... & Nestler, E. J. (2003). Regulation of RGS proteins by chronic morphine in rat locus coeruleus. *European Journal of Neuroscience*, *17*(5): 971-980.

Goldstein, A. V. R. A. M., & Goldstein, D. B. (1968). XIX. Enzyme expansion theory of drug tolerance and physical dependence. *Research Publications-Association for Research in Nervous and Mental Disease*, *46*: 265.

Gomes, I., Gupta, A., Filipovska, J., Szeto, H. H., Pintar, J. E., & Devi, L. A. (2004). A role for heterodimerization of μ and δ opiate receptors in enhancing morphine analgesia. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(14): 5135-5139.

Gonzalez, L. G., Portillo, E., Del Pozo, E., & Baeyens, J. M. (2001). Changes in [3 H] glibenclamide binding to mouse forebrain membranes during morphine tolerance. *European Journal of Pharmacology*, *418*(1): 29-37

González-Rodríguez, S., Hidalgo, A., Baamonde, A., & Menéndez, L. (2010). Involvement of Gi/o proteins and GIRK channels in the potentiation of morphine-induced spinal analgesia in acutely inflamed mice. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *381*(1): 59-71.

Goodman Jr, O. B., Krupnick, J. G., Santini, F., Gurevich, V. V., Penn, R. B., Gagnon, A. W., ... & Benovic, J. L. (1996). ß-Arrestin acts as a clathrin adaptor in endocytosis of the ß-adrenergic receptor. *Nature*, *383*: 3.

Greengard, P., & Nestler, E. J. (1984). *Protein phosphorylation in the nervous system*. New York, J. Wiley.

Greenwood, J. M., & Dragunow, M. (2010). M 3 muscarinic receptors promote cell survival through activation of the extracellular regulated kinase (ERK1/2) pathway. *European Journal of Pharmacology*, 640(1): 38-45.

Greenwood, J. M., & Dragunow, M. (2002). Muscarinic receptor-mediated phosphorylation of cyclic AMP response element binding protein in human neuroblastoma cells. *Journal of Neurochemistry*, 82(2): 389-397.

Griffin, W. J., & Lin, G. D. (2000). Chemotaxonomy and geographical distribution of tropane alkaloids. *Phytochemistry*, *53*(6): 623-637.

Groer, C. E., Schmid, C. L., Jaeger, A. M., & Bohn, L. M. (2011). Agonist-directed interactions with specific β-arrestins determine μ-opioid receptor trafficking, ubiquitination, and dephosphorylation. *Journal of Biological Chemistry*, *286*(36): 31731-31741.

Gros, R., Benovic, J. L., Tan, C. M., & Feldman, R. D. (1997). G-protein-coupled receptor kinase activity is increased in hypertension. *Journal of Clinical Investigation*, *99*(9): 2087.

Grynkiewicz, G., & Gadzikowska, M. (2008). Tropane alkaloids as medicinally useful natural products and their synthetic derivatives as new drugs. *Pharmacological Reports*, *60*(4): 439-463.

Guo, M. L., Mao, L. M., & Wang, J. Q. (2010). Modulation of M4 muscarinic acetylcholine receptors by interacting proteins. *Neuroscience Bulletin*, *26*(6): 469-473.

Gupta, P., & Prywes, R. (2002). ATF1 phosphorylation by the ERK MAPK pathway is required for epidermal growth factor-induced c-jun expression. *Journal of Biological Chemistry*, *277*(52): 50550-50556.

Gurevich, V. V., Chen, C. Y., Kim, C. M., & Benovic, J. L. (1994). Visual arrestin binding to rhodopsin. Intramolecular interaction between the basic N terminus and acidic C terminus of arrestin may regulate binding selectivity. *Journal of Biological Chemistry*, *269*(12): 8721-8727.

Haab, F., Stewart, L., & Dwyer, P. (2004). Darifenacin, an M 3 selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. *European Urology*, *45*(4): 420-429.

Hadcock, J. R., & Malbon, C. C. (1993). Agonist regulation of gene expression of adrenergic receptors and G proteins. *Journal of Neurochemistry*, *60*(1): 1-9.

Haller, V. L., Bernstein, M. A., & Welch, S. P. (2008). Chronic morphine treatment decreases the Ca V 1.3 subunit of the L-type calcium channel. *European Journal of Pharmacology*, *578*(2): 101-107.

Hamilton, S. L., Codina, J., Hawkes, M. J., Yatani, A., Sawada, T., Strickland, F. M., ... & Stefani, E. (1991). Evidence for direct interaction of Gs alpha with the Ca2+ channel of skeletal muscle. *Journal of Biological Chemistry*, *266*(29): 19528-19535.

Harada, H., Ueda, H., Wada, Y., Katada, T., Ui, M., & Satoh, M. (1989). Phosphorylation of μ-opioid receptors—a putative mechanism of selective uncoupling of receptor—Gi interaction, measured with low-Km CTPase and nucleotide-sensitive agonist binding. *Neuroscience Letters*, *100*(1-3): 221-226.

Harada, K., Matsuoka, H., Miyata, H., Matsui, M., & Inoue, M. (2015). Identification of muscarinic receptor subtypes involved in catecholamine secretion in adrenal medullary chromaffin cells by genetic deletion. *British Journal of Pharmacology*, *172*(5): 1348-1359.

Harborne, J. B. (1993). Biochemistry of plant pollination. *Introduction to Ecological Biochemistry*, 36-70.

Harisiadis, L., Miller, R. C., Hall, E. J., & Borek, C. (1978). A vitamin A analogue inhibits radiation-induced oncogenic transformation. *Nature*, 274: 486-487.

Hashimoto, T., & Yamada, Y. (1987). Purification and characterization of hyoscyamine 6β-hydroxylase from root cultures of *Hyoscyamus niger L.* *European Journal of Biochemistry*, *164*(2): 277-285.

Hausdorff, W. P., Caron, M. G., & Lefkowitz, R. J. (1990). Turning off the signal: desensitization of beta-adrenergic receptor function. *The Official Journal of the Federation of American Societies for Experimental Biology*, *4*(11): 2881-2889.

Hayashi, A., Seki, N., Hattori, A., Kozuma, S., & Saito, T. (1999). PKCν, a new member of the protein kinase C family, composes a fourth subfamily with PKCμ. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, *1450*(1): 99-106.

He, L., Fong, J., von Zastrow, M., & Whistler, J. L. (2002). Regulation of opioid receptor trafficking and morphine tolerance by receptor oligomerization. *Cell*, *108*(2): 271-282.

Hegnauer, R. (1981). Chemotaxonomy of Erythroxylaceae (including some Ethnobotanical notes on Old World species). *Journal of Ethnopharmacology*, 3(2): 279–292

Hofford, R. S., Hodgson, S. R., Roberts, K. W., Bryant, C. D., Evans, C. J., & Eitan, S. (2009). Extracellular signal-regulated kinase activation in the amygdala mediates elevated plus maze behavior during opioid withdrawal. *Behavioural Pharmacology*, *20*(7): 576-583.

Honda, K., Harada, A., Takano, Y., & Kamiya, H. O. (2000). Involvement of M3 muscarinic receptors of the spinal cord in formalin-induced nociception in mice. *Brain Research*, *859*(1): 38-44.

Huang, K. P. (1989). The mechanism of protein kinase C activation. *Trends in Neurosciences*, *12*(11): 425-432.

Iacovelli, L., Sallese, M., Mariggiò, S., & De Blasi, A. (1999). Regulation of G-protein-coupled receptor kinase subtypes by calcium sensor proteins. *Official Journal of the Federation of American Societies for Experimental Biology*, *13*(1): 1-8.

Igarashi, M., & Ohko, K. (2009). Proteins involved in the presynaptic functions. In *Handbook of Neurochemistry and Molecular Neurobiology* (pp. 45-62). Springer US.

Ignatova, E. G., Belcheva, M. M., Bohn, L. M., Neuman, M. C., & Coscia, C. J. (1999). Requirement of receptor internalization for opioid stimulation of

mitogen-activated protein kinase: biochemical and immunofluorescence confocal microscopic evidence. *Journal of Neuroscience*, *19*(1): 56-63.

Ilham, A. M., Suryani, S. A., Syarifah, M. S., Murni, Y. N., Asiah, O., Norhayati, I., & Sahira, H. L. Evaluating the effects of *Erythroxylum Cuneatum Forma Cuneatum* (miq.) Kurz (Chinta Mula) in morphine addicted rats.

Ingram, S. L., & Williams, J. T. (1996). Modulation of the hyperpolarization-activated current (Ih) by cyclic nucleotides in guinea-pig primary afferent neurons. *Journal of Physiology*, *492*(1): 97-106.

Inturrisi, C. E. (2002). Clinical pharmacology of opioids for pain. *Clinical Journal of Pain*, *18*(4): S3-S13.

Jahn, R., Lang, T., & Südhof, T. C. (2003). Membrane fusion. *Cell*, *112*(4): 519-533.

Jamil, M. F. A., Subki, M. F. M., Lan, T. M., Majid, M. I. A., & Adenan, M. I. (2013). The effect of mitragynine on cAMP formation and mRNA expression of mu-opioid receptors mediated by chronic morphine treatment in SK–N–SH neuroblastoma cell. *Journal of Ethnopharmacology*, *148*(1): 135-143.

Jan, L. Y., & Jan, Y. N. (1997). Receptor-regulated ion channels. *Current Opinion in Cell Biology*, *9*(2): 155-160.

Ji, R. R. (2004). Peripheral and central mechanisms of inflammatory pain, with emphasis on MAP kinases. *Current Drug Targets-Inflammation & Allergy*, *3*(3): 299-303.

Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A., & Dworkin, R. H. (2010). The prevalence of chronic pain in United States adults: results of an Internet-based survey. *Journal of Pain*, *11*(11): 1230-1239.

Johnson, E. E., Christie, M. J., & Connor, M. (2006b). The role of opioid receptor phosphorylation and trafficking in adaptations to persistent opioid treatment. *Neurosignals*, *14*(6): 290-302.

Johnson, E. E, Oldfield, S., Braksator, E., Gonzalez-cuello, A., Couch, D., Hall, K. J., … Henderson, G. (2006a). Agonist-selective mechanisms of -opioid receptor desensitization in human embryonic kidney 293 cells. *Molecular Pharmacology*, *70*(2): 676–685.

Jolas, T., Nestler, E. J., & Aghajanian, G. K. (1999). Chronic morphine increases GABA tone on serotonergic neurons of the dorsal raphe nucleus: association with an up-regulation of the cyclic AMP pathway. *Neuroscience*, *95*(2): 433-443.

Kalso, E., Edwards, J. E., Moore, R. A., & McQuay, H. J. (2004). Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*, *112*(3): 372-380.

Kanchanapoom, T., Sirikatitham, A., Otsuka, H., & Ruchirawat, S. (2006). Cuneatoside, a new megastigmane diglycoside from E*rythroxylum cuneatum* Blume: Note. *Journal of Asian Natural Products Research*, *8*(8): 747-751.

Kauer, J. A. (2004). Learning mechanisms in addiction: synaptic plasticity in the ventral tegmental area as a result of exposure to drugs of abuse. *Annual Review of Physiology*, *66*: 447-475.

Kawasaki, Y., Kohno, T., Zhuang, Z. Y., Brenner, G. J., Wang, H., Van Der Meer, … & Ji, R. R. (2004). Ionotropic and metabotropic receptors, protein kinase A, protein kinase C, and Src contribute to C-fiber-induced ERK activation and cAMP response element-binding protein phosphorylation in dorsal horn neurons, leading to central sensitization. *Journal of Neuroscience*, *24*(38): 8310-8321.

Keiser, M. J., Roth, B. L., Armbruster, B. N., Ernsberger, P., Irwin, J. J., & Shoichet, B. K. (2007). Relating protein pharmacology by ligand chemistry. *Nature Biotechnology*, *25*(2): 197-206.

Keller, M., Tränkle, C., She, X., Pegoli, A., Bernhardt, G., Buschauer, A., & Read, R. W. (2015). M2 Subtype preferring dibenzodiazepinone-type muscarinic receptor ligands: Effect of chemical homo-dimerization on orthosteric (and allosteric?) binding. *Bioorganic and Medicinal Chemistry*, 23 (14): 397-3990.

Khokhlatchev, A. V., Canagarajah, B., Wilsbacher, J., Robinson, M., Atkinson, M., Goldsmith, E., & Cobb, M. H. (1998). Phosphorylation of the MAP kinase ERK2 promotes its homodimerization and nuclear translocation. *Cell*, *93*(4): 605-615.

Kieffer, B. L., & Gavériaux-Ruff, C. (2002). Exploring the opioid system by gene knockout. *Progress in Neurobiology*, *66*(5): 285-306.

Kim, K. S., Lee, K. W., Lee, K. W., Im, J. Y., Yoo, J. Y., Kim, … & Han, P. L. (2006). Adenylyl cyclase type 5 (AC5) is an essential mediator of morphine action. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(10): 3908-3913.

Kirchhausen, T. (1999). Adaptors for clathrin-mediated traffic. *Annual Review of Cell and Developmental Biology*, *15*(1): 705-732.

Kittler, J. T., Delmas, P., Jovanovic, J. N., Brown, D. A., Smart, T. G., & Moss, S. J. (2000). Constitutive endocytosis of GABAA receptors by an association

with the adaptin AP2 complex modulates inhibitory synaptic currents in hippocampal neurons. *Journal of Neuroscience*, *20*(21): 7972-7977.

Ko, L., Cardona, G. R., Henrion-Caude, A., & Chin, W. W. (2002). Identification and characterization of a tissue-specific coactivator, GT198, that interacts with the DNA-binding domains of nuclear receptors. *Molecular and Cellular Biology*, *22*(1): 357-369.

Koch, T., & Höllt, V. (2008). Role of receptor internalization in opioid tolerance and dependence. *Pharmacology and Therapeutics*, *117*(2): 199-206.

Koch, T., Kroslak, T., Averbeck, M., Mayer, P., Schröder, H., Raulf, E., & Höllt, V. (2000). Allelic variation S268P of the human μ-opioid receptor affects both desensitization and G protein coupling. *Molecular Pharmacology*, *58*(2): 328-334.

Koch, T., Widera, A., Bartzsch, K., Schulz, S., Brandenburg, L. O., Wundrack, N., … & Höllt, V. (2005). Receptor endocytosis counteracts the development of opioid tolerance. *Molecular Pharmacology*, *67*(1): 280-287.

Kolch, W. (2005). Coordinating ERK/MAPK signalling through scaffolds and inhibitors. *Nature Reviews Molecular Cell Biology*, *6*(11): 827-837.

Koob, G. F., & Le Moal, M. (2002). Neurobiology of drug addiction. *Stages and Pathways of Drug Involvement: Examining the Gateway Hypothesis*: 337-361.

Koob, G. F., & Le Moal, M. (2005). *Neurobiology of Addiction*. Academic Press.

Koob, G. F., & Le Moal, M. (2008). Addiction and the brain anti-reward system. *Annual Review Psychology*, *59*(1): 29-53.

Kosterlitz, H. W., Corbett, A. D., Gillan, M. G., McKnight, A. T., Paterson, S. J., & Robson, L. E. (1986). Recent developments in bioassay using selective ligands and selective in vitro preparations. *Natural Institute on Drug Abuse Research Monograph*, *70*: 223-235.

Krapivinsky, G., Krapivinsky, L., Manasian, Y., Ivanov, A., Tyzio, R., Pellegrino, C., ... & Medina, I. (2003). The NMDA receptor is coupled to the ERK pathway by a direct interaction between NR2B and RasGRF1. *Neuron*, *40*(4): 775-784.

Krupnick, J. G., & Benovic, J. L. (1998). The role of receptor kinases and arrestins in G protein-coupled receptor regulation. *Annual Review of Pharmacology and Toxicology*, *38*(1): 289-319.

Krupnick, J. G., Gurevich, V. V., Schepers, T., Hamm, H. E., & Benovic, J. L. (1994). Arrestin-rhodopsin interaction. Multi-site binding delineated by peptide inhibition. *Journal of Biological Chemistry*, *269*(5): 3226-3232.

Kushwaha, A. K., Sangwan, N. S., Trivedi, P. K., Negi, A. S., Misra, L., & Sangwan, R. S. (2013). Tropine forming tropinone reductase gene from *Withania somnifera (Ashwagandha)*: Biochemical characteristics of the recombinant enzyme and novel physiological overtones of tissue-wide gene expression patterns. *Public Library of Science One*, 8(9): e74777.

Larsen, K. E., Schmitz, Y., Troyer, M. D., Mosharov, E., Dietrich, P., Quazi, A. Z., ... & Stefanis, L. (2006). α-Synuclein overexpression in PC12 and chromaffin cells impairs catecholamine release by interfering with a late step in exocytosis. *Journal of Neuroscience*, *26*(46): 11915-11922.

Law, P. Y., Hom, D. S., & Loh, H. H. (1984). Down-regulation of opiate receptor in neuroblastoma x glioma NG108-15 hybrid cells. Chloroquine promotes accumulation of tritiated enkephalin in the lysosomes. *Journal of Biological Chemistry*, *259*(7): 4096-4104.

Law, P. Y., & Loh, H. H. (1999). Regulation of opioid receptor activities. *Journal of Pharmacology and Experimental Therapeutics*, *289*(2): 607-624.

Law, P. Y., Wong, Y. H., & Loh, H. H. (2000). Molecular mechanisms and regulation of opioid receptor signaling. *Annual Review of Pharmacology and Toxicology*, *40*(1): 389-430.

Le Merrer, J., Becker, J. A., Befort, K., & Kieffer, B. L. (2009). Reward processing by the opioid system in the brain. *Physiological Reviews*, *89*(4): 1379-1412.

Leavitt, S. B. (2003). Methadone dosing & safety in the treatment of opioid addiction. In *Addiction Treatment Forum*, 12(2): 1-8

Lee, K. W., Hong, J. H., Choi, I. Y., Che, Y., Lee, J. K., Yang, S. D., … & Han, P. L. (2002). Impaired D2 dopamine receptor function in mice lacking type 5 adenylyl cyclase. *Journal of Neuroscience*, *22*(18): 7931-7940.

Leppert, W. (2009). The role of methadone in cancer pain treatment–a review. *International Journal of Clinical Practice*, *63*(7): 1095-1109.

Lefkowitz, R. J. (1998). G protein-coupled receptors III. New roles for receptor kinases and β-arrestins in receptor signaling and desensitization. *Journal of Biological Chemistry*, *273*(30): 18677-18680.

Liang, Y., Li, Q. F., Zhang, X. Y., Shi, S. L., & Jing, G. J. (2009). Differential expression of nuclear matrix proteins during the differentiation of human

neuroblastoma SK-N-SH cells induced by retinoic acid. *Journal of Cellular Biochemistry*, *106*(5): 849-857.

Lin, X., Wang, Q., Ji, J., & Yu, L. C. (2010). Role of MEK-ERK pathway in morphine-induced conditioned place preference in ventral tegmental area of rats. *Journal of Neuroscience Research*, *88*(7): 1595-1604.

Licata, S. C., Schmidt, H. D., & Pierce, R. C. (2004). Suppressing calcium/calmodulin-dependent protein kinase II activity in the ventral tegmental area enhances the acute behavioural response to cocaine but attenuates the initiation of cocaine-induced behavioural sensitization in rats. *European Journal of Neuroscience*, *19*(2): 405-414.

Liu, J. P. (1996). Protein kinase C and its substrates. *Molecular and Cellular Endocrinology*, *116*(1): 1-29.

Liu, J. G., & Anand, K. J. S. (2001). Protein kinases modulate the cellular adaptations associated with opioid tolerance and dependence. *Brain Research Reviews*, *38*(1): 1-19.

Liu, J. G., Liao, X. P., Gong, Z. H., & Qin, B. Y. (1999). Methadone-induced desensitization of the δ-opioid receptor is mediated by uncoupling of receptor from G protein. *European Journal of Pharmacology*, *374*(2): 301-308.

Lohse, M. J., Andexinger, S., Pitcher, J., Trukawinski, S., Codina, J., Faure, J. P., ... & Lefkowitz, R. J. (1992). Receptor-specific desensitization with purified proteins. Kinase dependence and receptor specificity of beta-arrestin and arrestin in the beta 2-adrenergic receptor and rhodopsin systems. *Journal of Biological Chemistry*, *267*(12): 8558-8564.

Lohse, M. J., Benovic, J. L., Caron, M. G., & Lefkowitz, R. J. (1990). Multiple pathways of rapid beta 2-adrenergic receptor desensitization. Delineation with specific inhibitors. *Journal of Biological Chemistry*, *265*(6): 3202-3211.

Lombet, A., Zujovic, V., Kandouz, M., Billardon, C., Carvajal-Gonzalez, S., Gompel, A., & Rostène, W. (2001). Resistance to induced apoptosis in the human neuroblastoma cell line SK-N-SH in relation to neuronal differentiation. *European Journal of Biochemistry*, *268*(5): 1352-1362.

Lotharius, J., & Brundin, P. (2002). Pathogenesis of Parkinson's disease: dopamine, vesicles and α-synuclein. *Nature Reviews Neuroscience*, *3*(12): 932-942.

Lounasmaa, M., & Tamminen, T. (1993). In The Alkaloids; Cordell, GA, Ed. *Academic Press: San Diego*, *44*: 1113.

Lu, L., Grimm, J. W., Shaham, Y., & Hope, B. T. (2003). Molecular neuroadaptations in the accumbens and ventral tegmental area during the first 90 days of forced abstinence from cocaine self-administration in rats. *Journal of Neurochemistry*, *85*(6): 1604-1613.

Ludwig, M. (2005). *Dendritic neurotransmitter release*. Springer Science & Business Media.

Luttrell, L. M., Ferguson, S. S. G., Daaka, Y., Miller, W. E., Maudsley, S., Della Rocca, G. J., … & Lefkowitz, R. J. (1999). β-Arrestin-dependent formation of β2 adrenergic receptor-Src protein kinase complexes. *Science*, *283*(5402): 655-661.

Luttrell, L. M., Roudabush, F. L., Choy, E. W., Miller, W. E., Field, M. E., Pierce, K. L., & Lefkowitz, R. J. (2001). Activation and targeting of extracellular signal-regulated kinases by β-arrestin scaffolds. *Proceedings of the National Academy of Sciences*, *98*(5): 2449-2454.

Ma, S., Li, X. Y., Gong, N., & Wang, Y. X. (2015). Contributions of spinal d-amino acid oxidase to chronic morphine-induced hyperalgesia. *Journal of Pharmaceutical and Biomedical Analysis*, *116*: 131-138.

Macey, T. A., Bobeck, E. N., Hegarty, D. M., Aicher, S. A., Ingram, S. L., & Morgan, M. M. (2009). Extracellular signal-regulated kinase 1/2 activation counteracts morphine tolerance in the periaqueductal gray of the rat. *Journal of Pharmacology and Experimental Therapeutics*, *331*(2): 412-418.

Mack, K. A. Centers for Disease Control and Prevention (CDC). (2013). Drug-Induced Deaths—United States, 1999–2010. *MMWR Surveill Summ*, *62* (Suppl 3), 161-163.

Mamiya, T., Noda, Y., Ren, X., Hamdy, M., Furukawa, S., Kameyama, T., ... & Nabeshima, T. (2001). Involvement of cyclic AMP systems in morphine physical dependence in mice: prevention of development of morphine dependence by rolipram, a phosphodiesterase 4 inhibitor. *British Journal of Pharmacology*, *132*(5): 1111-1117.

Manfredi, P. L., Foley, K. M., Payne, R., Houde, R., & Inturrisi, C. E. (2003). Parenteral methadone: an essential medication for the treatment of pain. *Journal of Pain and Symptom Management*, *26*(2): 687-688.

Martí, M. D., Milanés, M. V., & Laorden, M. L. (2003). Implication of the signal transduction pathways in the enhancement of noradrenaline turnover induced by morphine withdrawal in the heart. *European Journal of Pharmacology*, *471*(2): 113-119.

Martinez, J., Moeller, I., Erdjument-Bromage, H., Tempst, P., & Lauring, B. (2003). Parkinson's disease-associated α-synuclein is a calmodulin substrate. *Journal of Biological Chemistry*, *278*(19): 17379-17387.

Martini, L., & Whistler, J. L. (2007). The role of mu opioid receptor desensitization and endocytosis in morphine tolerance and dependence. *Current Opinion in Neurobiology*, *17*(5): 556-564.

Matsuoka, I., Suzuki, Y., Defer, N., Nakanishi, H., & Hanoune, J. (1997). Differential expression of type I, II, and V adenylyl cyclase gene in the postnatal developing rat brain. *Journal of Neurochemistry*, *68*(2): 498-506.

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systemic Reviews*, *3*(3).

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2014). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systemic Reviews*. Issue 2.

Mayer, D. J., Mao, J., & Price, D. D. (1995). The development of morphine tolerance and dependence is associated with translocation of protein kinase C. *Pain*, *61*(3): 365-374.

Mayer, D. J., Mao, J., Holt, J., & Price, D. D. (1999). Cellular mechanisms of neuropathic pain, morphine tolerance, and their interactions. *Proceedings of the National Academy of Sciences*, *96*(14): 7731-7736.

McClung, C. A., Nestler, E. J., & Zachariou, V. (2005). Regulation of gene expression by chronic morphine and morphine withdrawal in the locus ceruleus and ventral tegmental area. *Journal of Neuroscience*, *25*(25): 6005-6015.

McLean, S., & Twomey, F. (2015). Methods of rotation from another strong opioid to methadone for the management of cancer pain: A systematic review of the available evidence. *Journal of Pain and Symptom Management*. 50(2): 248-259.

McManus, O. B. (1991). Calcium-activated potassium channels: regulation by calcium. *Journal of Bioenergetics and Biomembranes*, *23*(4): 537-560.

Mercadante, S., Porzio, G., Ferrera, P., Fulfaro, F., Aielli, F., Verna, L.,… & Mangione, S. (2008). Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. *European Journal of Pain*, *12*(8): 1040-1046.

Merriman, R. L., & Bertram, J. S. (1979). Reversible inhibition by retinoids of 3-methylcholanthrene-induced neoplastic transformation in C3H/10T½ clone 8 cells. *Cancer Research*, *39*(5): 1661-1666.

Mestek, A., Hurley, J. H., Bye, L. S., Campbell, A. D., Chen, Y., Tian, M. I. N. G. T. I. N. G., ... & Yu, L. (1995). The human mu opioid receptor: modulation of functional desensitization by calcium/calmodulin-dependent protein kinase and protein kinase C. *Journal of Neuroscience*, *15*(3): 2396-2406.

Millan, M. J. (2002). Descending control of pain. *Progress in Neurobiology*, *66*(6): 355-474.

Mirzaii-Dizgah, I., Ojaghi, R., Sadeghipour-Roodsari, H. R., Karimian, S. M., & Sohanaki, H. (2009). Attenuation of morphine withdrawal signs by low level laser therapy in rats. *Behavioural Brain Research*, *196*(2): 268-270.

Miyatake, M., Rubinstein, T. J., McLennan, G. P., Belcheva, M. M., & Coscia, C. J. (2009). Inhibition of EGF-induced ERK/MAP kinase-mediated astrocyte proliferation by μ opioids: integration of G protein and β-arrestin 2-dependent pathways. *Journal of Neurochemistry*, *110*(2): 662-674.

Morgan, C., Muetzelfeldt, L., Muetzelfeldt, M., Nutt, D., & Curran, H. (2009). Harms associated with psychoactive substances: findings of the UK National Drug Survey. *Journal of Psychopharmacology*, *24*(2): 147-153.

Moriya, H., Takagi, Y., Nakanishi, T., Hayashi, M., Tani, T., & Hirotsu, I. (1999). Affinity profiles of various muscarinic antagonists for cloned human muscarinic acetylcholine receptor (mAChR) subtypes and mAChRs in rat heart and submandibular gland. *Life Sciences*, *64*(25): 2351-2358.

Moro, O., Lameh, J., & Sadee, W. (1993). Serine-and threonine-rich domain regulates internalization of muscarinic cholinergic receptors. *Journal of Biological Chemistry*, *268*(10): 6862-6865.

Morphine Addiction and Treatment - Futures of Palm Beach. (2016). *Futures of Palm Beach*. Retrieved 20 August 2016, from https://www.futuresofpalmbeach.com/addictions/morphine-addiction/withdrawal/

Movsesian, M. A., & Bristow, M. R. (2005). Alterations in cAMP-Mediated Signaling and Their Role in the Pathophysiology of Dilated Cardiomyopathy. *Current Topics in Developmental Biology*, *68*: 25-48.

Moyse, E., Marcel, D., Leonard, K., & Beaudet, A. (1997). Electron microscopic distribution of mu opioid receptors on noradrenergic neurons of the locus coeruleus. *European Journal of Neuroscience*, *9*(1): 128-139.

Mu, Y., Otsuka, T., Horton, A. C., Scott, D. B., & Ehlers, M. D. (2003). Activity-dependent mRNA splicing controls ER export and synaptic delivery of NMDA receptors. *Neuron*, *40*(3): 581-594.

Muller, D. L., & Unterwald, E. M. (2004). In vivo regulation of extracellular signal-regulated protein kinase (ERK) and protein kinase B (Akt) phosphorylation by acute and chronic morphine. *Journal of Pharmacology and Experimental Therapeutics*, *310*(2): 774-782.

Nakai, T., Hayashi, M., Ichihara, K., Wakabayashi, H., & Hoshi, K. (2002). Noradrenaline release in rat locus coeruleus is regulated by both opioid andα 2-adrenoceptors. *Pharmacological Research*, *45*(5): 407-412.

Narita, M., Aoki, T., Ozaki, S., Yajima, Y., & Suzuki, T. (2001a). Involvement of protein kinase Cγ isoform in morphine-induced reinforcing effects. *Neuroscience*, *103*(2): 309-314.

Narita, M., Funada, M., & Suzuki, T. (2001b). Regulations of opioid dependence by opioid receptor types. *Pharmacology and Therapeutics*, *89*(1): 1-15.

Narita, M., Makimura, M., Feng, Y., Hoskins, B., & Ho, I. K. (1994). Influence of chronic morphine treatment on protein kinase C activity: comparison with butorphanol and implication for opioid tolerance. *Brain Research*, *650*(1): 175-179.

Narita, M., Matsumura, Y., Ozaki, S., Ise, Y., Yajima, Y., & Suzuki, T. (2004). Role of the calcium/calmodulin-dependent protein kinase ii (CaMKII) in the morphine-induced pharmacological effects in the mouse. *Neuroscience*, *126*(2): 415-421.

Naruse, K., & King, G. L. (2000). Protein kinase C and myocardial biology and function. *Circulation Research*, *86*(11): 1104-1106.

Neal, B. S., & Sparber, S. B. (1986). Ketanserin and pirenperone attenuate acute morphine withdrawal in rats. *European Journal of Pharmacology*, *132*(2): 299-304.

Nehmad, R., Nadler, H., & Simantov, R. (1982). Effects of acute and chronic morphine treatment of calmodulin activity of rat brain. *Molecular Pharmacology*, *22*(2): 389-394.

Nemani, V. M., Lu, W., Berge, V., Nakamura, K., Onoa, B., Lee, M. K., ... & Edwards, R. H. (2010). Increased expression of α-synuclein reduces neurotransmitter release by inhibiting synaptic vesicle reclustering after endocytosis. *Neuron*, *65*(1): 66-79.

Nestler, E. J. (1992). Molecular mechanisms of drug addiction. *Journal of Neuroscience*, *12*(7): 2439-2450.

Nestler, E. J. (1996). Under siege: the brain on opiates. *Neuron*, *16*(5): 897-900.

Nestler, E. J. (2001). Molecular basis of long-term plasticity underlying addiction. *Nature Reviews Neuroscience*, *2*(2): 119-28.

Nestler, E. J. (2004a). Historical review: molecular and cellular mechanisms of opiate and cocaine addiction. *Trends in Pharmacological Sciences*, *25*(4): 210-218.

Nestler, E. J. (2004b). Molecular mechanisms of drug addiction. *Neuropharmacology*, *47*: 24-32.

Nestler, E. J., & Aghajanian, G. K. (1997). Molecular and cellular basis of addiction. *Science*, *278*(5335): 58-63.

Nestler, E. J., & Tallman, J. F. (1988). Chronic morphine treatment increases cyclic AMP-dependent protein kinase activity in the rat locus coeruleus. *Molecular Pharmacology*, *33*(2): 127-132.

Niikura, K., Narita, M., Butelman, E. R., Kreek, M. J., & Suzuki, T. (2010). Neuropathic and chronic pain stimuli downregulate central μ-opioid and dopaminergic transmission. *Trends in Pharmacological Sciences*, *31*(7): 299-305.

Nishizuka, Y. (1992). Intracellular signaling by hydrolysis of phospholipids and activation of protein kinase C. *Science*, *258*(5082): 607-614.

Nishizuka, Y. (1995). Protein kinase C and lipid signaling for sustained cellular responses. *The Official Journal of the Federation of American Societies for Experimental Biology*, *9*(7): 484-496.

Niwa, Y., & Haji, A. (2011). M3-receptor activation counteracts opioid-mediated apneusis, but the apneusis per se is not necessarily related to an impaired M3 mechanism in rats. *Life Sciences*, *89*(19): 685-690.

Nunez, C., Laorden, M. L., & Milanés, M. V. (2007). Regulation of serine (Ser)-31 and Ser40 tyrosine hydroxylase phosphorylation during morphine withdrawal in the hypothalamic paraventricular nucleus and nucleus tractus solitarius-A2 cell group: role of ERK1/2. *Endocrinology*, *148*(12): 5780-5793.

O'Brien, C. P., Childress, A. R., McLellan, A. T., & Ehrman, R. (1992). Classical conditioning in drug-dependent humans. *Annals of the New York Academy of Sciences*, *654*(1): 400-415.

O'Neill, E., & Kolch, W. (2004). Conferring specificity on the ubiquitous Raf/MEK signalling pathway. *British Journal of Cancer*, *90*(2): 283-288.

Onetti, C. G., Garcia, U., Valdiosera, R. F., & Arechiga, H. (1990). Ionic currents in crustacean neurosecretory cells. *Journal of Neurophysiology*, *64*(5): 1514-1526.

Ozaki, S., Narita, M., Iino, M., Miyoshi, K., & Suzuki, T. (2003). Suppression of the morphine-induced rewarding effect and G-protein activation in the lower midbrain following nerve injury in the mouse: involvement of G-protein-coupled receptor kinase 2. *Neuroscience*, *116*(1): 89-97.

Pacifici, R., di Carlo, S., Bacosi, A., Pichini, S., & Zuccaro, P. (2000). Pharmacokinetics and cytokine production in heroin and morphine-treated mice. *International Journal of Immunopharmacology*, *22*(8): 603-614.

Pagès, G., Guérin, S., Grall, D., Bonino, F., Smith, A., Anjuere, F., ... & Pouysségur, J. (1999). Defective thymocyte maturation in p44 MAP kinase (Erk 1) knockout mice. *Science, 286*(5443): 1374-1377.

Parent, J. L., Labrecque, P., Orsini, M. J., & Benovic, J. L. (1999). Internalization of the TXA2 receptor α and β isoforms. Role of the differentially spliced COOH terminus in agonist-promoted receptor internalization. *Journal of Biological Chemistry*, *274*(13): 8941-8948.

Parsadaniantz, S. M., Rivat, C., Rostène, W., & Réaux-Le Goazigo, A. (2015). Opioid and chemokine receptor crosstalk: a promising target for pain therapy? *Nature Reviews Neuroscience*, *16*(2): 69-78.

Pasternak, G.W., *The Opiate Receptors.* New York, NY: Humana Press/Springer. 2011

Payens J.P.D.W. (1958). Erythroxylaceae. In: Van Steenis CGGJ, ed. Flora Malesiana, Vol. 5. Leyden: P. Noordhoff Ltd., 548-552.

Pellegrini-Giampietro, D. E., Bacciottini, L., Carla, V., & Moroni, F. (1988). Morphine withdrawal in cortical slices: suppression by Ca2+-channel inhibitors of abstinence-induced [3H]-noradrenaline release. *British Journal of Pharmacology*, *93*(3): 535-540.

Pitcher, J. A., Freedman, N. J., & Lefkowitz, R. J. (1998). G protein-coupled receptor kinases. *Annual Review of Biochemistry*, *67*(1): 653-692.

Plant, T. D., & Schaefer, M. (2003). TRPC4 and TRPC5: receptor-operated Ca 2+-permeable nonselective cation channels. *Cell Calcium*, *33*(5): 441-450.

Plowman, T., & Rivier, L. (1983). Cocaine and cinnamoylcocaine content of *Erythroxylum* species. *Annals of Botany*, *51*(5): 641-659.

Polakiewicz, R. D., Schieferl, S. M., Dorner, L. F., Kansra, V., & Comb, M. J. (1998). A mitogen-activated protein kinase pathway is required for μ-opioid receptor desensitization. *Journal of Biological Chemistry*, *273*(20): 12402-12406.

Portoghese, P. S., & Lunzer, M. M. (2003). Identity of the putative δ 1-opioid receptor as a δ–κ heteromer in the mouse spinal cord. *European Journal of Pharmacology*, *467*(1): 233-234.

Pothos, E., Rada, P., Mark, G. P., & Hoebel, B. G. (1991). Dopamine microdialysis in the nucleus accumbens during acute and chronic morphine, naloxone-precipitated withdrawal and clonidine treatment. *Brain Research*, *566*(1-2): 348-350.

Prayong, P., Barusrux, S., & Weerapreeyakul, N. (2008). Cytotoxic activity screening of some indigenous Thai plants. *Fitoterapia*, *79*(7-8): 598–601.

Pronin, A. N., & Benovic, J. L. (1997). Regulation of the G protein-coupled receptor kinase GRK5 by protein kinase C. *Journal of Biological Chemistry*, *272*(6): 3806-3812.

Pronin, A. N., Satpaev, D. K., Slepak, V. Z., & Benovic, J. L. (1997). Regulation of G protein-coupled receptor kinases by calmodulin and localization of the calmodulin binding domain. *Journal of Biological Chemistry*, *272*(29): 18273-18280.

PubChem Structure. (2016). *Pubchem.ncbi.nlm.nih.gov*. Retrieved 20 August 2016, from https://pubchem.ncbi.nlm.nih.gov/image/fl.html?cid=5288826

PubChem Structure. (2016). *Pubchem.ncbi.nlm.nih.gov*. Retrieved 20 August 2016, from https://pubchem.ncbi.nlm.nih.gov/image/fl.html?cid=4095

Purves, D., Augustine, G., Fitzpatrick, D., Katz, L., LaMantia, A., McNamara, J., & Williams, S. (2001). Nuclear Signaling. *Sinauer Associates*. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK10929

Quetglas, S., Iborra, C., Sasakawa, N., De Haro, L., Kumakura, K., Sato, K., Leveque, C., & Seagar, M. (2002). Calmodulin and lipid binding to synaptobrevin regulates calcium-dependent exocytosis. *European Molecular Biology Organization (EMBO) Journal*, *21*(15): 3970-3979.

Rada, P. V., Mark, G. P., Taylor, K. M., & Hoebel, B. G. (1996). Morphine and naloxone, ip or locally, affect extracellular acetylcholine in the accumbens and prefrontal cortex. *Pharmacology Biochemistry and Behavior*, *53*(4): 809-816.

Raehal, K. M., & Bohn, L. M. (2005). Mu opioid receptor regulation and opiate responsiveness. *American Association of Pharmaceutical Scientists Journal*, *7*(3): E587-E591.

Rahim, R. T., Adler, M. W., Meissler, J. J., Cowan, A., Rogers, T. J., Geller, E. B., & Eisenstein, T. K. (2002). Abrupt or precipitated withdrawal from morphine induces immunosuppression. *Journal of Neuroimmunology*, *127*(1): 88-95.

Rang, H. P., Dale, M. M., Ritter, J. M., & Moore, P. K. (2003). Pharmacology. 5 [sup] th ed. *Edinburgh: Churchill Livingstone*, 585-587.

Raskin, I., Ribnicky, D. M., Komarnytsky, S., Ilic, N., Poulev, A., Borisjuk, N., … & Fridlender, B. (2002). Plants and human health in the twenty-first century. *TRENDS in Biotechnology*, *20*(12): 522-531.

Rinner, I., & Schauenstein, K. (1993). Detection of choline-acetyltransferase activity in lymphocytes. *Journal of Neuroscience Research*, 35(2): 188-191.Rivier, L. (1981). Analysis of alkaloids in leaves of cultivated Erythroxylum and characterization of alkaline substances used during coca chewing, *Journal of Ethnopharmacology, 3*(2): 313–335.

Robinson, F. L., Whitehurst, A. W., Raman, M., & Cobb, M. H. (2002). Identification of novel point mutations in ERK2 that selectively disrupt binding to MEK 1. *Journal of Biological Chemistry*, *277*(17): 14844-14852.

Robles, L. I., Barrios, M., & Baeyens, J. (1994). ATP-sensitive K+ channel openers inhibit morphine withdrawal. *European Journal of Pharmacology*, *251*(1): 113-115.

Rosenblum, A., Parrino, M., Schnoll, S. H., Fong, C., Maxwell, C., Cleland, C. M., ... & Haddox, J. D. (2007). Prescription opioid abuse among enrollees into methadone maintenance treatment. *Drug and Alcohol Dependence*, *90*(1): 64-71.

Roy, S., Wang, J., Gupta, S., Charboneau, R., Loh, H. H., & Barke, R. A. (2004). Chronic morphine treatment differentiates T helper cells to Th2 effector cells by modulating transcription factors GATA 3 and T-bet. *Journal of Neuroimmunology*, *147*(1): 78-81.

Sadovsky, R. (2000). Public health issue: Methadone maintenance therapy. *American Family Physician*, *62*(2): 428-432.

Sadja, R., Alagem, N., & Reuveny, E. (2003). Gating of GIRK channels: details of an intricate, membrane-delimited signaling complex. *Neuron*, *39*(1): 9-12.

SAMHSA Releases Behavioral Health, United States, 2012. (2013). *PS*, *64*(12), 1281-1281. http://dx.doi.org/10.1176/appi.ps.6412news1

Samways, D. S., & Henderson, G. (2006). Opioid elevation of intracellular free calcium: possible mechanisms and physiological relevance. *Cellular Signalling*, *18*(2): 151-161.

Scavone, J. L., Sterling, R. C., & Van Bockstaele, E. J. (2013). Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. *Neuroscience*, *248*: 637-654.

Scheggi, S., Masi, F., Tagliamonte, A., Gambarana, C., Tolu, P., & De Montis, M. G. (2000). Rats sensitized to morphine are resistant to the behavioral effects of an unavoidable stress. *Brain Research*, *853*(2): 290-298.

Schmidt, L. S., Thomsen, M., Weikop, P., Dencker, D., Wess, J., Woldbye, D. P., ... & Fink-Jensen, A. (2011). Increased cocaine self-administration in M4 muscarinic acetylcholine receptor knockout mice. *Psychopharmacology*, *216*(3): 367-378.

Schulz, R., Eisinger, D. A., & Wehmeyer, A. (2004). Opioid control of MAP kinase cascade. *European Journal of Pharmacology*, *500*(1): 487-497.

Schulz, S., & Höllt, V. (1998). Opioid withdrawal activates MAP kinase in locus coeruleus neurons in morphine-dependent rats in vivo. *European Journal of Neuroscience*, *10*(3): 1196-1201.

Schwarz, T. L., Tempel, B. L., Papazian, D. M., Jan, Y. N., & Jan, L. Y. (1988). Multiple potassium-channel components are produced by alternative splicing at the Shaker locus in Drosophila. *Nature*, *331*(6152): 137-142.

Sculptoreanu, A., Scheuer, T., & Catterall, W. A. (1993). Voltage-dependent potentiation of L-type Ca2+ channels due to phosphorylation by cAMP-dependent protein kinase. *Nature*, *364*(6434): 240-243.

Sculptoreanu, A., Rotman, E., Takahashi, M., Scheuer, T., & Catterall, W. A. (1993b). Voltage-dependent potentiation of the activity of cardiac L-type calcium channel alpha 1 subunits due to phosphorylation by cAMP-dependent protein kinase. *Proceedings of the National Academy of Sciences*, *90*(21): 10135-10139.

Seow Li, L. (2015). *Antioxidant and anti-inflammatory properties of Erythroxylum cuneatum leaf alkaloid extract*. (Unpublished Bachelor dissertation), Cyberjaya University College of Medical Sciences (CUCMS).

Sharma, S. K., Klee, W. A., & Nirenberg, M. (1975). Dual regulation of adenylate cyclase accounts for narcotic dependence and tolerance. *Proceedings of the National Academy of Sciences*, *72*(8): 3092-3096.

Sharma, S. K., Klee, W. A., & Nirenberg, M. (1977). Opiate-dependent modulation of adenylate cyclase. *Proceedings of the National Academy of Sciences*, *74*(8): 3365-3369.

Sheehan, M. J., Hayes, A. G., & Tyers, M. B. (1988). Lack of evidence for ε-opioid receptors in the rat vas deferens. *European Journal of Pharmacology*, *154*(3): 237-245.

Shekhar, A., Potter, W. Z., Lightfoot, J., Lienemann D Pharm, J., Dube, S., … & Felder, C. C. (2008). Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *American Journal of Psychiatry*, *165*(8): 1033-1039.

Shoji, Y., Delfs, J., & Williams, J. T. (1999). Presynaptic inhibition of GABAB-mediated synaptic potentials in the ventral tegmental area during morphine withdrawal. *Journal of Neuroscience*, *19*(6): 2347-2355.

Shonesy, B. C., Jalan-Sakrikar, N., Cavener, V. S., & Colbran, R. J. (2014). CaMKII: a molecular substrate for synaptic plasticity and memory. *Program in Molecular Biology and Translational Science*, *122*: 61-87.

Shulman, H. (1993). The multifunctional Ca2/calmodulin-dependent protein kinases. *Current Opinion in Cell Biology*, *5*(2): 247-253.

Sibley, D. R., Strasser, R. H., Benovic, J. L., Daniel, K., & Lefkowitz, R. J. (1986). Phosphorylation/dephosphorylation of the beta-adrenergic receptor regulates its functional coupling to adenylate cyclase and subcellular distribution. *Proceedings of the National Academy of Sciences*, *83*(24): 9408-9412.

Simonin, F., Valverde, O., Smadja, C., Slowe, S., Kitchen, I., Dierich, A., … & Kieffer, B. L. (1998). Disruption of the κ-opioid receptor gene in mice enhances sensitivity to chemical visceral pain, impairs pharmacological actions of the selective κ-agonist U-50,488 H and attenuates morphine withdrawal. *European Molecular Biology Organization (EMBO) Journal*, *17*(4): 886-897.

SK-N-SH ATCC ® HTB-11™ Homo sapiens brain; derived from meta. (2016). *Atcc.org*. Retrieved 9 August 2016, from https://www.atcc.org/products/all/HTB-11.aspx#generalinformation

Smart, D., Hirst, R. A., Hirota, K., Grandy, D. K., & Lambert, D. G. (1997). The effects of recombinant rat μ-opioid receptor activation in CHO cells on

phospholipase C, [Ca^{2+}]i and adenylyl cyclase. *British Journal of Pharmacology*, *120*(6): 1165-1171.

Smart, D., & Lambert, D. G. (1995). Desensitization of the μ-opioid activation of phospholipase C in SH-SY5Y cells: the role of protein kinases C and A and Ca2+-activated K+ currents. *British Journal of Pharmacology*, *116*(6): 2655-2660.

Smith, R. S., Hu, R., DeSouza, A., Eberly, C. L., Krahe, K., Chan, W., & Araneda, R. C. (2015). Differential muscarinic modulation in the olfactory bulb. *Journal of Neuroscience*, *35*(30): 10773-10785.

Smith, F. L., Javed, R., Elzey, M. J., Welch, S. P., Selley, D., Sim-Selley, L., & Dewey, W. L. (2002). Prolonged reversal of morphine tolerance with no reversal of dependence by protein kinase C inhibitors. *Brain Research*, *958*(1): 28-35.

Sporn, M. B., Dunlop, N. M., Newton, D. L., & Smith, J. M. (1976, May). Prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). *In Federation Proceedings* (Vol. 35, No. 6, pp. 1332-1338).

Stefano, G. B., Burrill, J. D., Labur, S., Blake, J., & Cadet, P. (2005). Regulation of various genes in human leukocytes acutely exposed to morphine: expression microarray analysis. *American Journal of Case Reports*, *11*(5): MS35-MS42.

Steidl, S., Miller, A. D., Blaha, C. D., & Yeomans, J. S. (2011). M (5) muscarinic receptors mediate striatal dopamine activation by ventral tegmental morphine and pedunculopontine stimulation in mice. *Public Library of Science One*, *6*(11): e27538.

Stein, C. (1999). *Opioids in pain control: basic and clinical aspects*. Cambridge University Press.

Stein, C., Schäfer, M., & Machelska, H. (2003). Attacking pain at its source: new perspectives on opioids. *Nature Medicine*, *9*(8): 1003.

Sudhof, T. C. (2004). The synaptic vesicle cycle. *Annual Review of Neuroscience*, *27*: 509-547.

Sullivan, N. R., Leventhal, L., Harrison, J., Smith, V. A., Cummons, T. A., Spangler, T. B., … & Jones, P. G. (2007). Pharmacological characterization of the muscarinic agonist ($_3R$, $_4R$)-$_3$-($_3$-hexylsulfanyl-pyrazin-2-yloxy)-1-aza-bicyclo [2.2.1] heptane (WAY-132983) in *in vitro* and *in vivo* models of chronic pain. *Journal of Pharmacology and Experimental Therapeutics*, *322*(3): 1294-1304.

Sutton, R. B., Fasshauer, D., Jahn, R., & Brunger, A. T. (1998). Crystal structure of a SNARE complex involved in synaptic exocytosis at 2.4 Å resolution. *Nature*, *395*(6700): 347-353.

Sweitzer, S. M., Wong, S. M., Tjolsen, A., Allen, C. P., Mochly-Rosen, D., & Kendig, J. J. (2004). Exaggerated nociceptive responses on morphine withdrawal: roles of protein kinase C ε and γ. *Pain*, *110*(1): 281-289.

Tang, T., Stevens, B. A., & Cox, B. M. (1996). Opioid regulation of intracellular free calcium in cultured mouse dorsal root ganglion neurons. *Journal of Neuroscience Research*, *44*(4): 338-343.

Tanoue, T., Adachi, M., Moriguchi, T., & Nishida, E. (2000). A conserved docking motif in MAP kinases common to substrates, activators and regulators. *Nature Cell Biology*, *2*(2): 110-116.

Tapocik, J. D., Letwin, N., Mayo, C. L., Frank, B., Luu, T., Achinike, O., …, & Lee, N. H. (2009). Identification of candidate genes and gene networks specifically associated with analgesic tolerance to morphine. *Journal of Neuroscience*, *29*(16): 5295-5307.

Taussig, R., Iniguez-Lluhi, J. A., & Gilman, A. G. (1993). Inhibition of adenylyl cyclase by Gi alpha. *Science*, *261*(5118): 218-221.

Tempel, A. (1991). Visualization of μ opiate receptor downregulation following morphine treatment in neonatal rat brain. *Developmental Brain Research*, *64*(1): 19-26.

Tempel, B. L., Jan, Y. N., & Jan, L. Y. (1988). Cloning of a probable potassium channel gene from mouse brain. *Nature, 332*(6167): 837-839.

The Plant Observatory. (2016). *Natureloveyou.sg*. Retrieved 7 June 2016, from http://www.natureloveyou.sg/

Thomas, G. M., & Huganir, R. L. (2004). MAPK cascade signalling and synaptic plasticity. *Nature Reviews Neuroscience*, *5*(3): 173-183.

Tokuyama, S., Feng, Y., Wakabayashi, H., & Ho, K. (1995). Possible involvement of protein kinases in physical dependence on opioids: studies using protein kinase inhibitors, H-7 and H-8. *European Journal of Pharmacology*, *284*(1): 101-107.

Trang, T., Sutak, M., Quirion, R., & Jhamandas, K. (2003). Spinal administration of lipoxygenase inhibitors suppresses behavioural and neurochemical manifestations of naloxone-precipitated opioid withdrawal. *British Journal of Pharmacology*, *140*(2): 295-304.

Tsantoulas, C., & McMahon, S. B. (2014). Opening paths to novel analgesics: the role of potassium channels in chronic pain. *Trends in Neurosciences*, *37*(3): 146-158.

Tso, P. H., & Wong, Y. H. (2001). Role of extracellular signal-regulated kinases in opioid-induced adenylyl cyclase superactivation in human embryonic kidney 293 cells. *Neuroscience Letters*, *316*(1): 13-16.

Tso, P. H., & Wong, Y. H. (2003). Molecular basis of opioid dependence: role of signal regulation by G-proteins. *Clinical and Experimental Pharmacology and Physiology*, *30*(5-6): 307-316.

Tyler, V. E. (1999). Phytomedicines : Back to the Future. *Journal of Natural Products*, *62*(11): 1589–1592.

Uchiyama, T., & Chess-Williams, R. (2004). Muscarinic receptor subtypes of the bladder and gastrointestinal tract. *Journal of Smooth Muscle Research*, 40(6): 237-247.

Vacek, T. P., Moshal, K. S., Metreveli, N., Tyagi, N., Sen, U., Rosenberger, D., & Tyagi, S. C. (2008). Cardiac Gαs and Gαi Modulate Sympathetic Versus Parasympathetic Mechanisms in Hyperhomocysteinemia. In *Signal Transduction in the Cardiovascular System in Health and Disease* (pp. 51-66). Springer US.

Valjent, E., Pascoli, V., Svenningsson, P., Paul, S., Enslen, H., Corvol, J. C., … & Girault, J. A. (2005). Regulation of a protein phosphatase cascade allows convergent dopamine and glutamate signals to activate ERK in the striatum. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(2): 491-496.

Van den Oever, M. C., Goriounova, N. A., Li, K. W., Van der Schors, R. C., Binnekade, R., Schoffelmeer, A. N., ... & De Vries, T. J. (2008). Prefrontal cortex AMPA receptor plasticity is crucial for cue-induced relapse to heroin-seeking. *Nature Neuroscience*, *11*(9): 1053-1058.

Van Ree, J. M., Niesink, R. J., Van Wolfswinkel, L., Ramsey, N. F., Van Furth, W. R., Vanderschuren, L. J., ... & Van den Berg, C. L. (2000). Endogenous opioids and reward. *European Journal of Pharmacology*, *405*(1): 89-101.

Vekrellis, K., Rideout, H. J., & Stefanis, L. (2004). Neurobiology of α-synuclein. *Molecular Neurobiology*, *30*(1): 1-21.

Ventayol, P., Busquets, X., & García-Sevilla, J. A. (1997). Modulation of immunoreactive protein kinase C-α and β isoforms and G proteins by acute

and chronic treatments with morphine and other opiate drugs in rat brain. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *355*(4): 491-500.

Vigano, D., Rubino, T., Di Chiara, G., Ascari, I., Massi, P., & Parolaro, D. (2003). μ opioid receptor signaling in morphine sensitization. *Neuroscience*, *117*(4): 921-929.

Vogel, Z., Barg, J., Attali, B., & Simantov, R. (1990). Differential effect of μ, δ, and κ ligands on G protein α subunits in cultured brain cells. *Journal of Neuroscience Research*, *27*(1): 106-111.

Volkow, N. D., Fowler, J. S., Wang, G. J., & Goldstein, R. Z. (2002). Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. *Neurobiology of Learning and Memory*, *78*(3): 610-624.

von Zastrow, M., & Williams, J. T. (2012). Modulating neuromodulation by receptor membrane traffic in the endocytic pathway. *Neuron*, *76*(1): 22-32.

Voon, P., Hayashi, K., Milloy, M. J., Nguyen, P., Wood, E., Montaner, J., & Kerr, T. (2015). Pain among high-risk patients on methadone maintenance treatment. *Journal of Pain*, *16*(9): 887-894.

Wachholtz, A., & Gonzalez, G. (2014). Co-morbid pain and opioid addiction: Long term effect of opioid maintenance on acute pain. *Drug and Alcohol Dependence*, *145*: 143-149

Wadel, K., Neher, E., & Sakaba, T. (2007). The coupling between synaptic vesicles and Ca 2+ channels determines fast neurotransmitter release. *Neuron*, *53*(4): 563-575.

Wainford, R. D., Kurtz, K., & Kapusta, D. R. (2007). Central G {alpha} i and G {alpha} o protein inhibition by pertussis toxin (PTX) blocks the cardiovascular depressor but not diuretic response to central Nociceptin/Orphanin FQ (N/OFQ) administration in conscious Sprague-Dawley rats. *The Federation of American Societies for Experimental Biology Journal*, *21*(6): A785.

Waldhoer, M., Bartlett, S. E., & Whistler, J. L. (2004). Opioid receptors. *Annual Review of Biochemistry*, *73*(1): 953-990.

Walker, J. K., Premont, R. T., Barak, L. S., Caron, M. G., & Shetzline, M. A. (1999). Properties of secretin receptor internalization differ from those of the β2-adrenergic receptor. *Journal of Biological Chemistry*, *274*(44): 31515-31523.

Wang, H. Y., Frankfurt, M., & Burns, L. H. (2008). High-affinity naloxone binding to filamin A prevents mu opioid Receptor–Gs coupling underlying opioid tolerance and dependence. *Public Library of Science One*, *3*(2):1554.

Wang, F., Zeng, X., Zhu, Y., Ning, D., Liu, J., Liu, C., ... & Zhu, D. (2015). Effects of thyroxine and donepezil on hippocampal acetylcholine content, acetylcholinesterase activity, synaptotagmin-1 and SNAP-25 expression in hypothyroid adult rats. *Molecular Medicine Reports, 11*(2): 775-782.

Wang, Z., Shi, H., & Wang, H. (2004). Functional M3 muscarinic acetylcholine receptors in mammalian hearts. *British Journal of Pharmacology*, *142*(3): 395-408.

Way, K. J., Chou, E., & King, G. L. (2000). Identification of PKC-isoform-specific biological actions using pharmacological approaches. *Trends in Pharmacological Sciences*, *21*(5): 181-187.

Welch, S. P., & Bass, P. P. (1995). Modulation of free intracellular calcium levels [(Ca++) i] in brain and spinal cord of morphine-tolerant rats and mice. *Pharmacology Biochemistry and Behavior*, *51*(1): 57-63.

Wellbrock, C., Karasarides, M., & Marais, R. (2004). The RAF proteins take centre stage. *Nature Reviews Molecular Cell Biology*, *5*(11): 875-885.

Wersinger, C., & Sidhu, A. (2003). Attenuation of dopamine transporter activity by α-synuclein. *Neuroscience Letter, 340*(3): 189-192.

Wesam, R. K., Ghanya, a N., Mizaton, H. H., Ilham, M., & Aishah, a. (2013). Assessment of genotoxicity and cytotoxicity of standardized aqueous extract from leaves of *Erythroxylum cuneatum* in human HepG2 and WRL68 cells line. *Asian Pacific Journal of Tropical Medicine*, *6*(10): 811–816.

Wesson, D. R., & Ling, W. (2003). The clinical opiate withdrawal scale (COWS). *Journal of Psychoactive Drugs*, *35*(2): 253-259.

Weston-Green, K., Huang, X. F., Lian, J., & Deng, C. (2012). Effects of olanzapine on muscarinic M3 receptor binding density in the brain relates to weight gain, plasma insulin and metabolic hormone levels. *European Neuropsychopharmacology*, *22*(5): 364-373.

Whistler, J. L., Chuang, H. H., Chu, P., Jan, L. Y., & von Zastrow, M. (1999). Functional dissociation of μ opioid receptor signaling and endocytosis: implications for the biology of opiate tolerance and addiction. *Neuron*, *23*(4): 737-746.

Whistler, J. L., & Von Zastrow, M. (1998). Morphine-activated opioid receptors elude desensitization by β-arrestin. *Proceedings of the National Academy of Sciences*, *95*(17): 9914-9919.

Wilding, T. J., Womack, M. D., & McCleskey, E. W. (1995). Fast, local signal transduction between the mu opioid receptor and Ca2+ channels. *Journal of Neuroscience*, *15*(5): 4124-4132.

Williams, J. T., Christie, M. J., & Manzoni, O. (2001). Cellular and synaptic adaptations mediating opioid dependence. *Physiological Reviews*, *81*(1): 299-343.

Willoughby, D., & Cooper, D. M. (2007). Organization and Ca2+ regulation of adenylyl cyclases in cAMP microdomains. *Physiological Reviews*, *87*(3): 965-1010.

Wink, M. (1999). Introduction: biochemistry, role and biotechnology of secondary products. In M. Wink (ed.), *Biochemistry of Secondary Product Metabolism* (pp. 1-16). CRC Press, Boca Raton, FL.

Wise, R. A., & Bozarth, M. A. (1987). A psychomotor stimulant theory of addiction. *Psychological Review*, *94*(4): 469.

Wolfman, C., Fin, C., Dias, M., Bianchin, M., Da Silva, R. C., Schmitz, P. K., … & Izquierdo, I. (1994). Intrahippocampal or intraamygdala infusion of KN62, a specific inhibitor of calcium/calmodulin-dependent protein kinase II, causes retrograde amnesia in the rat. *Behavioral and Neural Biology*, *61*(3): 203-205.

Xing, J., Ginty, D. D., & Greenberg, M. E. (1996). Coupling of the RAS-MAPK pathway to gene activation by RSK2, a growth factor-regulated CREB kinase. *Science*, *273*(5277): 959.

Xu, N. J., Yu, Y. X., Zhu, J. M., Liu, H., Shen, L., Zeng, R., Zhang, X., & Pei, G. (2004). Inhibition of SNAP-25 phosphorylation at Ser187 is involved in chronic morphine-induced down-regulation of SNARE complex formation. *Journal of Biological Chemistry*, *279*(39): 40601-40608.

Yabaluri, N., & Medzihradsky, F. (1997). Down-regulation of μ-opioid receptor by full but not partial agonists is independent of G protein coupling. *Molecular Pharmacology*, *52*(5): 896-902.

Yamada, M., Basile, A. S., Fedorova, I., Zhang, W., Duttaroy, A., Cui, Y., … & Wess, J. (2003). Novel insights into M 5 muscarinic acetylcholine receptor function by the use of gene targeting technology. *Life Sciences*, *74*(2): 345-353.

Yamada, K., & Inagaki, N. (2005). Neuroprotection by K ATP channels. *Journal of Molecular and Cellular Cardiology*, *38*(6): 945-949.

Yamamoto, H., Harris, R. A., Loh, H. H., & Way, E. L. (1978). Effects of acute and chronic morphine treatments on calcium localization and binding in brain. *Journal of Pharmacology and Experimental Therapeutics*, *205*(2): 255-264.

Yang, S. N., Huang, L. T., Wang, C. L., Chen, W. F., Yang, C. H., Lin, S. Z., ... & Tao, P. L. (2003). Prenatal administration of morphine decreases CREBSerine-133 phosphorylation and synaptic plasticity range mediated by glutamatergic transmission in the hippocampal CA1 area of cognitive-deficient rat offspring. *Hippocampus*, *13*(8): 915-921.

Yavich, L., Tanila, H., Vepsäläinen, S., & Jäkälä, P. (2004). Role of α-synuclein in presynaptic dopamine recruitment. *Journal of Neuroscience*, *24*(49): 11165-11170.

Yu, X., Mao, X., Blake, A. D., Li, W. X., & Chang, S. L. (2003). Morphine and endomorphins differentially regulate micro-opioid receptor mRNA in SHSY-5Y human neuroblastoma cells. *Journal of Pharmacology and Experimental Therapeutics*, *306*(2): 447–454.

Yu, V. C., & Sadée, W. (1988). Efficacy and tolerance of narcotic analgesics at the mu opioid receptor in differentiated human neuroblastoma cells. *Journal of Pharmacology and Experimental Therapeutics*, *245*(1): 350-355.

Yu, Y., Zhang, L., Yin, X., Sun, H., Uhl, G. R., & Wang, J. B. (1997). μ Opioid receptor phosphorylation, desensitization, and ligand efficacy. *Journal of Biological Chemistry*, *272*(46): 28869-28874.

Yuan, C. S., Foss, J. F., O'Connor, M., Osinski, J., Karrison, T., Moss, J., & Roizen, M. F. (2000). Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. *Journal of the American Medical Association, 283*(3): 367-372.

Zachariou, V., Liu, R., LaPlant, Q., Xiao, G., Renthal, W., Chan, G. C., … & Nestler, E. J. (2008). Distinct roles of adenylyl cyclases 1 and 8 in opiate dependence: behavioral, electrophysiological, and molecular studies. *Biological Psychiatry*, *63*(11): 1013-1021.

Zacny, J. P., Lichtor, J. L., Flemming, D., Coalson, D. W., & Thompson, W. K. (1994). A dose-response analysis of the subjective, psychomotor and physiological effects of intravenous morphine in healthy volunteers. *Journal of Pharmacology and Experimental Therapeutics*, *268*(1): 1-9

Zarrindast, M. R., Jafari, M. R., Shafaghi, B., & Djahanguiri, B. (2004). Influence of potassium channel modulators on morphine state-dependent memory of passive avoidance. *Behavioural Pharmacology*, *15*(2): 103-110.

Zhang, X., Bao, L., Arvidsson, U., Elde, R., & Hökfelt, T. (1997). Localization and regulation of the delta-opioid receptor in dorsal root ganglia and spinal cord of the rat and monkey: evidence for association with the membrane of large dense-core vesicles. *Neuroscience*, *82*(4): 1225-1242.

Zhang, S. Q., Bi, H. M., & Liu, C. J. (2007). Extraction of bio-active components from Rhodiola sachalinensis under ultrahigh hydrostatic pressure. *Separation and Purification Technology*, *57*(2): 277-282.

Zhang, L. C., & Buccafusco, J. J. (1998). Prevention of morphine-induced muscarinic (M2) receptor adaptation suppresses the expression of withdrawal symptoms. *Brain Research*, *803*(1): 114-121.

Zhang, L. C., & Buccafusco, J. J. (2000). Adaptive changes in M1 muscarinic receptors localized to specific rostral brain regions during and after morphine withdrawal. *Neuropharmacology*, *39*(10): 1720-1731.

Zhang, H. G., Cheng, Y. Q., Liu, Y., Zhou, J. Z., Jia, Y., Wang, X. Q., & Li, X. H. (2011). Gαq-protein carboxyl terminus imitation polypeptide GCIP-27 attenuates proliferation of vascular smooth muscle cells and vascular remodeling in spontaneously hypertensive rats. *Biological and Pharmaceutical Bulletin*, *34*(10): 1527-1532.

Zhang, J., Ferguson, S. S., Barak, L. S., Bodduluri, S. R., Laporte, S. A., Law, P. Y., & Caron, M. G. (1998). Role for G protein-coupled receptor kinase in agonist-specific regulation of μ-opioid receptor responsiveness. *Proceedings of the National Academy of Sciences*, *95*(12): 7157-7162.

Zhang, J., Ferguson, S. S., Barak, L. S., Ménard, L., & Caron, M. G. (1996). Dynamin and β-arrestin reveal distinct mechanisms for G protein-coupled receptor internalization. *Journal of Biological Chemistry*, *271*(31): 18302-18305.

Zhang, Y., Butelman, E. R., Schlussman, S. D., Ho, A., & Kreek, M. J. (2004). Effect of the endogenous κ opioid agonist dynorphin A (1–17) on cocaine-evoked increases in striatal dopamine levels and cocaine-induced place preference in C57BL/6J mice. *Psychopharmacology*, *172*(4): 422-429.

Zhang, Y., Chen, Q., & Yu, L. C. (2008). Morphine: a protective or destructive role in neurons? *Neuroscientist*, *14*(6): 561-570.

Zhang, Y., Xiong, W., Lin, X., Ma, X., & Yu, L. C. (2009). Receptor trafficking induced by μ-opioid-receptor phosphorylation. *Neuroscience and Biobehavioral Reviews*, *33*(8): 1192-1197.

Zhu, X., & Birnbaumer, L. (1996). G protein subunits and the stimulation of phospholipase C by Gs-and Gi-coupled receptors: Lack of receptor selectivity

of Galpha (16) and evidence for a synergic interaction between Gbeta gamma and the alpha subunit of a receptor activated G protein. *Proceedings of the National Academy of Sciences*, *93*(7): 2827-2831.

Ziolkowska, B., Gieryk, A., Bilecki, W., Wawrzczak-Bargiela, A., Wedzony, K., Chocyk, A., ... & Przewlocki, R. (2005). Regulation of α-synuclein expression in limbic and motor brain regions of morphine-treated mice. *Journal of Neuroscience*, *25*(20): 4996-5003.

Ziolkowska, B., Gieryk, A., Wawrzczak-Bargiela, A., Krowka, T., Kaminska, D., Korkosz, A., ... & Przewlocki, R. (2008). α-Synuclein expression in the brain and blood during abstinence from chronic alcohol drinking in mice. *Neuropharmacology*, *54*(8): 1239-1246.