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(54) Title: TREATMENT OF SCHIZOPHRENIA USING BETA-CARYOPHYLLENE AND CB2 RECEPTOR AGONISTS

(57) Abstract: Disclosed are compositions comprising beta-caryophyllene (BCP) for use in the treatment of schizophrenia, methods of making such compositions and methods of treating schizophrenia using BCP. Disclosed are also compositions comprising CB2 receptor agonists for use in the treatment of schizophrenia, methods of making such compositions and methods of treating schizophrenia using CB2 receptor agonists.



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TREATMENT OF SCHIZOPHRENIA USING BETA-CARYOPHYLLENE AND CB2 RECEPTOR AGONISTS

RELATED APPLICATION

5 The present application gains priority from U.S. Provisional Patent Application No. 61/612,411 filed 19 March 2012, which is included by reference as if fully set-forth herein.

FIELD AND BACKGROUND OF THE INVENTION

10 The invention, in some embodiments, relates to the field of therapy and more particularly, but not exclusively, to compositions comprising beta-caryophyllene (BCP), methods of making the compositions and methods using BCP, for the treatment of schizophrenia. The invention, in some embodiments, relates to the field of therapy and more particularly, but not exclusively, to compositions comprising Cannabinoid Receptor Type 2 (CB2) receptor agonists, methods of making the compositions and methods using CB2
15 receptor agonists for the treatment of schizophrenia.

 Schizophrenia affects about 1% of the population (Lewis & Lieberman, 2000), and genetic and environmental factors underlie the eventual eruption of the disease (Ross, 2006). Schizophrenia is often chronic, characterized by deterioration of social contact, cognitive deficits, anxiety and depression, resulting in suicide in about 10% of the schizophrenic
20 population (Lewis & Lieberman, 2000).

 Different subtypes of schizophrenia are defined according to the most significant and predominant characteristics present, as follows: Paranoid schizophrenia; Disorganized schizophrenia; Undifferentiated schizophrenia; Catatonic schizophrenia; and Residual schizophrenia.
25

SUMMARY OF THE INVENTION

 Some embodiments of the invention relate to compositions comprising beta-caryophyllene (BCP), methods of making the compositions and methods using BCP for the treatment of schizophrenia. Some embodiments of the invention relate to compositions
30 comprising Cannabinoid Receptor Type 2 (CB2) receptor agonists, methods of making the compositions and methods using CB2 receptor agonists for the treatment of schizophrenia.

 According to an aspect of some embodiments of the invention, there is provided a therapeutic composition comprising beta-caryophyllene (BCP) and a pharmaceutically effective carrier for use in treating schizophrenia. In some embodiments, the composition is

for use in the treatment of a human subject. In some embodiments, the composition is for use in the treatment of a non-human subject.

In some embodiments, the schizophrenia is selected from the group consisting of paranoid schizophrenia; disorganized schizophrenia; undifferentiated schizophrenia; catatonic schizophrenia; and residual schizophrenia.

In some embodiments, the treating comprises treating at least one symptom of schizophrenia selected from the group consisting of a negative symptom of schizophrenia and a positive symptom of schizophrenia.

In some embodiments, the pharmaceutically effective carrier comprises dimethyl sulfoxide (DMSO). In some such embodiments, the pharmaceutically effective carrier comprises DMSO, saline and Cremophor EL. In some such embodiments, the pharmaceutically effective carrier comprises DMSO, saline and Cremophor EL at a ratio of 1:0.6:18 Cremophor EL:DMSO:saline.

In some embodiments, a single discrete unit (e.g., a single tablet, capsule, metered liquid) of the composition comprises BCP at a weight in the range of from about 25 to about 100 mg.

In some embodiments, the composition is formulated as an injectable solution dosage form. In some embodiments, the injectable solution is configured to be administered by a route selected from the group consisting of intravenous injection, intramuscular injection, intradermal injection, intraperitoneal injection, intrathecal injection and subcutaneous injection.

In some embodiments, the composition is formulated as an orally-administrable dosage form. In some such embodiments, the composition is formulated in a dosage form selected from the group consisting of a tablet, a capsule, a dragee, a powder, granules, and an ingestible solution, especially a tablet or capsule.

In some embodiments, the composition further comprises at least one additional antipsychotic agent. In some such embodiments, at least one additional antipsychotic agent is selected from the group consisting of chlorpromazine, haloperidol, perphenazine, fluphenazine, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone, or combinations thereof.

According to an aspect of some embodiments of the invention, there is also provided the use of beta-caryophyllene (BCP) and a pharmaceutically effective carrier in the manufacture of a composition (also known as a medicament) for treating schizophrenia in a subject in need thereof. In some embodiments, the composition is configured for use in the

treatment of a human subject. In some embodiments, the composition is configured for use in the treatment of a non-human subject.

In some embodiments, the schizophrenia is selected from the group consisting of paranoid schizophrenia; disorganized schizophrenia; undifferentiated schizophrenia; catatonic schizophrenia; and residual schizophrenia.

In some embodiments, the treating comprises treating at least one symptom of schizophrenia selected from the group consisting of a negative symptom of schizophrenia and a positive symptom of schizophrenia.

In some embodiments, the pharmaceutically effective carrier comprises dimethyl sulfoxide (DMSO). In some such embodiments, the pharmaceutically effective carrier comprises DMSO, saline and Cremophor EL. In some such embodiments, the pharmaceutically effective carrier comprises DMSO, saline and Cremophor EL at a ratio of 1:0.6:18 Cremophor EL:DMSO:saline.

In some embodiments, a single discrete unit (e.g., a single tablet, capsule, metered liquid) of the composition that is manufactured comprises BCP at a weight in the range of from about 25 to about 100 mg.

In some embodiments, the composition is made as an injectable solution dosage form. In some embodiments, the injectable solution is configured to be administered by a route selected from the group consisting of intravenous injection, intramuscular injection, intradermal injection, intraperitoneal injection, intrathecal injection and subcutaneous injection.

In some embodiments, the composition is made as an orally-administrable dosage form. In some such embodiments, the dosage form selected from the group consisting of a tablet, a capsule, a dragee, a powder, granules, and an ingestible solution, especially a tablet or capsule.

In some embodiments, the composition further comprises at least one additional antipsychotic agent. In some such embodiments, at least one additional antipsychotic agent is selected from the group consisting of chlorpromazine, haloperidol, perphenazine, fluphenazine, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone, or combinations thereof.

According to an aspect of some embodiments of the present invention, there is also provided a method for treating schizophrenia in a subject in need thereof, the method comprising administering a therapeutic composition comprising beta-caryophyllene (BCP)

and a pharmaceutically effective carrier. In some embodiments, the subject is a human subject. In some embodiments, the subject is a non-human subject.

In some embodiments, the schizophrenia is selected from the group consisting of paranoid schizophrenia; disorganized schizophrenia; undifferentiated schizophrenia; catatonic
5 schizophrenia; and residual schizophrenia.

In some embodiments, the treating comprises treating at least one symptom of schizophrenia selected from the group consisting of a negative symptom of schizophrenia and a positive symptom of schizophrenia.

In some embodiments, the average daily amount of the BCP administered to the
10 subject is from about 0.4 mg/kg to about 2 mg/kg.

In some embodiments, the pharmaceutically effective carrier comprises dimethyl sulfoxide (DMSO). In some such embodiments, the pharmaceutically effective carrier comprises DMSO, saline and Cremophor EL. In some such embodiments, the pharmaceutically effective carrier comprises DMSO, saline and Cremophor EL at a ratio of
15 1:0.6:18 Cremophor EL:DMSO:saline.

In some embodiments, the administering comprises injecting the composition to the subject. In some embodiments, the injecting comprises injecting by a route selected from the group consisting of intravenous injection, intramuscular injection, intradermal injection, intraperitoneal injection, intrathecal injection and subcutaneous injection.

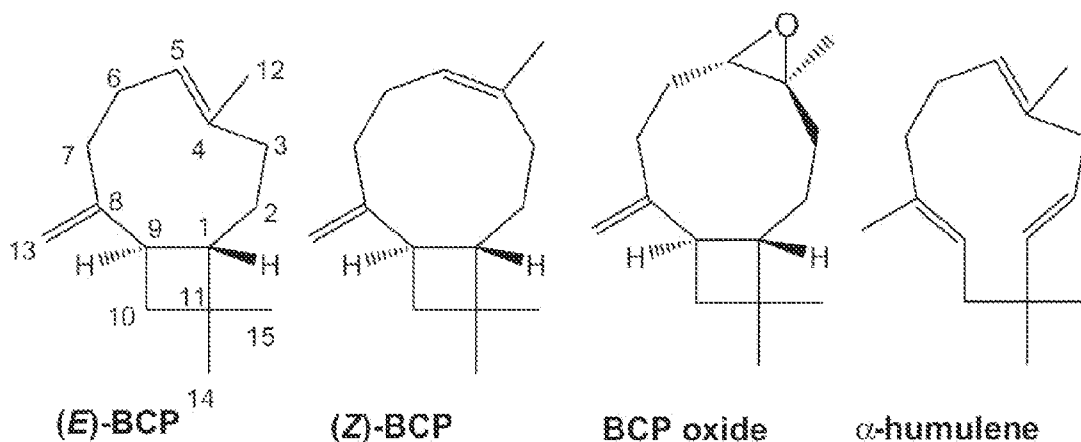
20 In some embodiments, the administering comprises orally administering the composition to the subject.

In some embodiments, the method further comprises co-administering at least one additional antipsychotic agent. In some such embodiments, the at least one additional antipsychotic agent is selected from the group consisting of chlorpromazine, haloperidol, perphenazine, fluphenazine, clozapine, risperidone, olanzapine, quetiapine, ziprasidone,
25 aripiprazole, and paliperidone, or combinations thereof.

In some such embodiments, the at least one additional antipsychotic agent is co-administered in a single dosage form together with the BCP. In some such embodiments, the at least one additional antipsychotic agent is co-administered in a dosage form separate from
30 the BCP. In some such embodiments, the co-administration comprises sequential or simultaneous administration. In some such embodiments, the sequential administration comprises administration of the at least one additional antipsychotic agent prior to administration of the BCP. In some such embodiments, the sequential administration

comprises administration of the at least one additional antipsychotic agent subsequent to administration of the BCP.

When found in nature, BCP (beta-caryophyllene) typically appears as a mixture of two pharmaceutically-active isomers E-BCP and Z-BCP, together with substantially inactive sesquiterpenes such as alpha-humulene and derivatives such as BCP oxide. Typically, natural sources include a greater proportion of E-BCP than Z-BCP.



For implementing the teachings herein, the BCP includes both E-BCP and Z-BCP, alone or in combination.

In some embodiments, the BCP used for implementing the teachings herein is at least 65%, at least 75%, at least 85% and even at least 95% by weight E-BCP. In some embodiments, the BCP is substantially pure (at least 99% by weight) E-BCP.

In some embodiments, the BCP used for implementing the teachings herein is at least 65%, at least 75%, at least 85% and even at least 95% by weight Z-BCP. In some embodiments, the BCP is substantially pure (at least 99% by weight) Z-BCP.

In some embodiments, the BCP used for implementing the teachings herein is at least 65%, at least 75%, at least 85% and even at least 95% by weight E-BCP and/or Z-BCP. In some embodiments, the BCP is substantially pure (at least 99% by weight) E-BCP and/or Z-BCP.

For example, in some embodiments the BCP used for implementing the teachings herein comprises 45-49% E-BCP, 45-49% Z-BCP, 1-5% BCP oxide and 1-5% alpha humulene.

For example, in some embodiments BCP used for implementing the teachings herein comprises 45-90% E-BCP, 5-30% Z-BCP, 1-5% BCP oxide and traces alpha humulene.

According to an aspect of some embodiments of the invention, there is also provided
5 a composition comprising a CB2 receptor agonist and a pharmaceutically effective carrier for use in treating schizophrenia.

According to an aspect of some embodiments of the invention, there is also provided a use of a composition comprising a CB2 receptor agonist and a pharmaceutically effective carrier in the manufacture of a composition for treating schizophrenia in a subject in need
10 thereof.

According to an aspect of some embodiments of the invention, there is also provided a method for the treating schizophrenia in a subject in need thereof, the method comprising administering a therapeutic composition comprising a CB2 receptor agonist and a pharmaceutically effective carrier.

15 Any suitable CB2 receptor agonist may be used in implementing the composition, the use or the method of treating, in some embodiments BCP and/or HU308. In some embodiments, the various features, options and embodiments are as explicitly discussed with reference to BCP.

In some embodiments, the teachings herein are applied to the treatment of human
20 subjects, for example, humans suffering from schizophrenia.

In some embodiments, the teachings herein are applied to the treatment of non-human animal subjects suffering from schizophrenia.

Unless otherwise defined, all technical and scientific terms used herein have the same
25 meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. In case of conflict, the specification, including definitions, takes precedence.

As used herein, the terms "comprising", "including", "having" and grammatical variants thereof are to be taken as specifying the stated features, integers, steps or components but do not preclude the addition of one or more additional features, integers,
30 steps, components or groups thereof.

As used herein, the indefinite articles "a" and "an" mean "at least one" or "one or more" unless the context clearly dictates otherwise.

As used herein, when a numerical value is preceded by the term "about", the term "about" is intended to indicate +/-10%.

As used herein, the term "treating" includes curing a condition, treating a condition, preventing a condition, treating symptoms of a condition, curing symptoms of a condition, ameliorating symptoms of a condition, treating effects of a condition, ameliorating effects of a condition, and preventing results of a condition

5 As used herein a "therapeutic composition" refers to a preparation of one or more of the active ingredients with other components such as pharmaceutically-acceptable carriers and excipients. The purpose of a therapeutic composition is to facilitate administration of an active ingredient to a subject.

10 The term "pharmaceutically acceptable carrier" refers to a carrier or a diluent that does not cause significant irritation to a subject and does not substantially abrogate the activity and properties of the administered active ingredients. An adjuvant is included under these phrases. The term "excipient" refers to an inert substance added to a therapeutic composition to further facilitate administration of an active ingredient.

15 Therapeutic compositions used in implementing the teachings herein may be formulated using techniques with which one of average skill in the art is familiar in a conventional manner using one or more pharmaceutically-acceptable carriers comprising excipients and adjuvants, which facilitate processing of the active ingredients into a pharmaceutical composition and generally includes mixing an amount of the active ingredients with the other components. Suitable techniques are described in "Remington's
20 Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition, which is incorporated herein by reference. For example, pharmaceutical compositions useful in implementing the teachings herein may be manufactured by one or more processes that are well known in the art, e.g., mixing, blending, homogenizing, dissolving, granulating, emulsifying, encapsulating, entrapping and lyophilizing processes.

25 Pharmaceutical compositions suitable for implementing the teachings herein include compositions comprising active ingredients in an amount effective to achieve the intended purpose (a therapeutically effective amount). Determination of a therapeutically effective amount is well within the capability of those skilled in the art, for example, is initially estimated from animal models such as monkey or pigs.

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BRIEF DESCRIPTION OF THE FIGURES

Some embodiments of the invention are described herein with reference to the accompanying figures. The description, together with the figures, makes apparent to a person having ordinary skill in the art how some embodiments of the invention may be practiced.

The figures are for the purpose of illustrative discussion and no attempt is made to show structural details of an embodiment in more detail than is necessary for a fundamental understanding of the invention. For the sake of clarity, some objects depicted in the figures are not to scale.

5 In the Figures:

FIGS. 1A and 1B relate to mouse body weight at PND 16-17: Figure 1A is a line graph showing changes in body weight at postnatal days 3 to 17 in mice treated with phencyclidine (PCP), PCP+BCP or control (vehicle) and Figure 1B is a bar graph showing body weight for the 3 groups at postnatal day 17;

10 FIGS. 2A-2C relate to open field test at PND 16-17: Figures 2A and 2B are line graphs showing ambulation (2A) and rearing (2B) at PND 16-17 and Figure 2C is a bar graph showing body weight at PND 17;

FIGS. 3A-3F relate to open field test at PND 16-17: Figures 3A and 3D are bar graphs showing body weight for males (3A) and females (3D), Figures 3B and 3E are line graphs showing ambulation in males (3E) and females (3F) and Figures 3C and 3F are line graphs showing rearing in males (3C) and females (3F);

FIGS. 4A-4F relate to open field test at PND 35-37: Figures 4A and 4D are bar graphs showing body weight for males (4A) and females (4D), Figures 4B and 4E are line graphs showing rearing in males (4B) and females (4E) and Figures 4C and 4F are line graphs showing ambulation in males (4C) and females (4F);

FIGS. 5A-5D relate to pre-pulse inhibition at age 8 weeks: Figures 5A and 5C are bar graphs showing response to startle for 8 week old males (5A) and females (5C); Figures 5B and 5D are line graphs showing percentage inhibition of prepulse inhibition for males (5B) and females (5D);

25 FIGS. 6A-6H relate to elevated plus maze test at age 13 weeks: female duration closed (6A), male duration closed (6B), female duration open (6C), male duration open (6D), female duration distal open (6E), male duration distal open (6F), female open/close duration (6G) and male open/close duration (6H);

FIGS. 7A -7I are bar graphs showing mRNA expression of cannabinoid receptors in 9 day old mice for glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in the left cortex (7A), right cortex (7B) and brain stem (7G); for Cannabinoid Receptor Type 1 (CB1) in the left cortex (7C), right cortex (7D) and brain stem (7H); and for CB2 in the left cortex (7E), right cortex (7F), and brain stem (7I) for control mice and mice treated with PCP;

FIG. 8 is a Table detailing the percentage change (%) relative to control animals of protein expression of cannabinoid receptors in 2 week old mice;

FIGS. 9A-9C are bar graphs showing protein expression of 67 kDa glutamic acid decarboxylase (GAD67)/actin in the left cortex (9A), right cortex (9B) and brain stem (9C) of 2-week old mice treated with saline or PCP;

FIGS. 9D-9F are bar graphs showing protein expression of 67 kDa glutamic acid decarboxylase (GAD67)/actin in the left cortex (9D), right cortex (9E) and brain stem (9F) of 9-day old mice treated with saline or PCP;

FIGS. 10A-10C relate to monoacylglycerol lipase (MGL) expression in 2 week old mice treated with saline or PCP: bar graph relating to the left cortex (10A), bar graph relating to the right cortex (10B) and Western blot (10C);

FIGS. 11A and 11B are schematic representations of the endocannabinoid synthesizing and degrading pathways as described in Anavi-Goffer, ChemBioChem 2009;

FIGS. 12A-12C relate to PND17 using a DMSO-based vehicle: line-graph showing male ambulation (12A), line-graph showing male rearing (12B) and line graph showing male body weight (12C);

FIGS. 13A-13C relate to PND16: line-graph showing body weight over PND 3-17 (13A), line-graph showing male and female ambulation (13B) and line-graph showing male and female rearing (13C);

FIGS. 14A-14E show results demonstrating that BCP treatment at adolescence reversed the effect of PCP on ambulation but did not affect body weight: line graph of body weight at PND 40-68 (14A), bar graph of female and male body weight at PND63 (14B), line graph of male ambulation at PND 63 (14D), line graph of female ambulation at PND 63 and line graph of male and female ambulation at PND 63;

FIGS. 15A-15C show results demonstrating that BCP treatment at adolescence reversed the effect of PCP on rearing: line graph of male and female rearing at PND63 (15A), line graph of male rearing at PND63 (15B) and line graph of female rearing at PND63 (15C);

FIGS. 16A-16C show results demonstrating that BCP treatment at adolescence reversed the effect of PCP on PPI: line graph of %PPI at PND68 (16A); bar graph of female startle response at PND68 (16B) and bar graph of male startle response at PND68 (16C);

FIGS. 17A-17C show results demonstrating that BCP treatment at adolescence reversed the effect of PCP on the response to tone (PPI test): line graph of response to tone at PND68 (17A); line graph of female response to tone at PND68 (17B) and line graph of male response to tone at PND68 (17C);

FIGS. 18A-18C show results demonstrating that BCP treatment at adolescence did not affect the startle response at the end of the PPI test: female startle response at PND 68 (18A), male startle response at PND 68 (18B) and all-mice startle response at PND68 (18C);

FIGS. 19A-19F show results demonstrating that BCP treatment at adolescence did not
5 reverse the effects of PCP in plus maze test: open/close duration at PND 64 (19A), open/(close+open) duration at PND 64 (19B), distal open/(close+open) duration at PND 64 (19C), open/close frequency at PND 64 (19D), open/(open+close) frequency at PND 64 (19E) and distal open/(open+close) frequency at PND 64 (19F);

FIGS. 20A-20E show results demonstrating that BCP treatment at adolescence
10 reversed the effects of PCP on the time spent in the hidden zone (behavior in the Phenotyper cage): bar graph of female hidden zone duration at PND 91 (20A), bar graph of male hidden zone duration at PND 91 (20B), bar graph of male and female hidden zone duration at PND 91 (20C), bar graph of male hidden zone frequency at PND 91 (20D) and bar graph of female hidden zone frequency at PND 91 (20E);

FIGS. 21A-21C show results demonstrating that BCP treatment at adolescence
15 reversed the effects of PCP on frequency of entries to the wheel (motor behavior in the Phenotyper cage: bar graph of female wheel zone frequency at PND 91 (21A), bar graph of male wheel zone frequency at PND 91 (21B) and bar graph of male and female wheel zone frequency at PND 91 (21C);

FIGS. 22A-22F show results demonstrating that BCP treatment at adolescence on the
20 time spent at drinking and food zones (Phenotyper cage): bar graph showing male food zone duration at PND91 (22A), bar graph showing female food zone duration at PND91 (22B), bar graph showing male and female food zone duration at PND91 (22C), bar graph showing male drink zone duration at PND91 (22D), bar graph showing female drink zone duration at
25 PND91 (22E) and bar graph showing male and female drink zone duration at PND91 (22F);

FIGS. 23A-23E show results demonstrating that BCP treatment at adolescence improved exploration and rearing behaviors of male PCP treated mice at PND 104: line graph of female ambulation at PND 104 (23A), line graph of male ambulation at PND 104 (23B), line graph of female rearing at PND 104 (23C), line graph of male rearing at PND 104 (23D)
30 and bar graph of male and female body weight at PND 104 (23E);

FIGS. 24A-24C show results demonstrating that BCP treatment at adolescence did not reverse the effect of PCT on grooming at PND104: bar graph of female grooming at PND 104 (24A), bar graph of male grooming at PND 104 (24B) and bar graph of male and female grooming at PND 104 (24C);

FIGS. 25A-25I show results demonstrating that BCP treatment at adolescence reversed the effect of PCP on attention at PND106 (PPI test): bar graph of female startle at PND 106 (25A), bar graph of male startle at PND 106 (25B), bar graph of male and female startle at PND 106 (25C), line graph of female response to tone of varying intensity (25D), line graph of female response to tone of varying intensity (25E), line graph of female response to tone of varying intensity (25F), line graph of % prepulse inhibition for females at PND 106 (25G), line graph of % prepulse inhibition for males at PND 106 (25H) and line graph of % prepulse inhibition for males and females at PND 106 (25I);

FIGS. 26A-26F show results demonstrating that BCP treatment at adolescence reversed the effect of PCP on frequency of entries to hidden zone (Phenotyper cage) at PND 105: bar graph of male hidden zone frequency at PND 105 (26A), bar graph of female hidden zone frequency at PND 105 (26B), bar graph of male and female hidden zone frequency at PND 105 (26C), bar graph of male wheel zone frequency at PND 105 (26D), bar graph of female wheel zone frequency at PND 105 (26E) and bar graph of male and female wheel zone frequency at PND 105 (26F);

FIGS. 27A-27E show results demonstrating that BCP treatment at adolescence reversed the effect of PCP on time spent at the hidden zone but not the time spent in the wheel zone (Phenotyper cage) at PND 105: bar graph of male hidden zone duration at PND 105 (27A), bar graph of female hidden zone duration at PND 105 (27B), bar graph of male wheel zone duration at PND 105 (27C), bar graph of female wheel zone duration at PND 105 (27D) and bar graph of male and female wheel zone duration at PND 105 (27E); and

FIGS. 28A-28B show results demonstrating that AM630 reversed the effect of BCP on PCP-induced inhibition of ambulation and rearing: line graph of male ambulation at 17 days (28A) and line graph of male rearing at 17 days (28B).

DESCRIPTION OF SOME EMBODIMENTS OF THE INVENTION

Some embodiments of the invention relate to compositions comprising beta-caryophyllene (BCP), methods of making the compositions and methods using BCP for the treatment of schizophrenia. Some embodiments of the invention relate to compositions comprising Cannabinoid Receptor Type 2 (CB2) receptor agonists, methods of making the compositions and methods using CB2 receptor agonists for the treatment of schizophrenia.

The principles, uses and implementations of the teachings herein may be better understood with reference to the accompanying description and figures. Upon perusal of the

description and figures present herein, one skilled in the art is able to implement the invention without undue effort or experimentation.

The Cannabinoid Receptor Type 2 (CB2) is a guanine nucleotide-binding protein (G protein)-coupled receptor that in humans is encoded by the *CNR2* gene.

5 Recent studies have identified the cannabinoid CB2 receptor in the brain. Up-regulation of CB2 receptor expression in the brain during central nervous system pathologies has been demonstrated for certain neurological diseases.

Beta-caryophyllene (BCP, CAS 87-44-5) is a CB2-receptor agonist (Gertsch et al. 2008, Anavi-Goffer et al., 2012). The fact that orally-administered BCP is absorbed by the
10 digestive tract and becomes systemically available and apparent substantial non-toxicity makes BCP attractive as a potential active pharmaceutical ingredient.

The role of CB2 receptor agonists in general, and BCP in particular, in the treatment of schizophrenia, has not previously been studied.

The Inventors have studied the effect of BCP in a murine model of schizophrenia,
15 produced by administration of the N-methyl-D-aspartic acid (NMDA) antagonist, phencyclidine (PCP). Administration of phencyclidine to rats (e.g. Josselyn and Vaccarino, 1998; Wang & Johnson, 2005; Ballmaier, 2007; Takahashi, 2006) or mice (e.g. Long, 2006; Hashimoto 2005) has been used as an animal model for schizophrenia. Phencyclidine may be administered acutely or chronically, during adulthood or during postnatal development, using
20 different dose ranges (2.5 mg/kg to 20 mg/kg). In order to induce chronic, long lasting schizophrenic-like behaviors and neurochemical changes in the endocannabinoid system, the Inventors have now developed a neonatal mouse model, based on a neonatal phencyclidine model previously described for rats (Takahashi, 2006). As the Inventors have extensively studied the endocannabinoid system in Sabra strain mice (Harlan, Israel), see for example
25 Fride 2005 and Fride 2007, these mice have been used in the present study.

The Inventors have found that following administration of PCP, the CB2 receptor expression level is selectively down-regulated in different brain areas. Furthermore, up-regulation of putative CB2 receptor expression has been detected in the right cortex and basal ganglia/diencephalon of mice which were neonatally treated with phencyclidine. These
30 results support some aspects of the teachings herein, where putative CB2 receptors are up-regulated in specific brain areas in schizophrenia.

Thus, according to an aspect of some embodiments of the teachings herein, there is provided a composition comprising beta-caryophyllene (BCP) and a pharmaceutically effective carrier for use in treating schizophrenia.

According to an aspect of some embodiments of the teachings herein, there is also provided the use of beta-caryophyllene (BCP) and a pharmaceutically effective carrier in the manufacture of a medicament for treating schizophrenia in a subject in need thereof.

In some embodiments, such a composition is configured for administration to a human subject. In some embodiments, such a composition is configured for administration to a non-human animal subject.

According to an aspect of some embodiments disclosed herein, there is also provided a method for treating schizophrenia in a subject in need thereof, the method comprising administering a pharmaceutically-effective amount of beta-caryophyllene (BCP) to the subject. In some embodiments, the subject is a human subject. In some embodiments, the subject is a non-human animal.

The efficacy of the methods and compositions according to the teachings herein are demonstrated in the experimental section hereinbelow.

According to some embodiments, the compositions and methods of treatments disclosed herein are useful for treating one or more of paranoid schizophrenia; disorganized schizophrenia; undifferentiated schizophrenia; catatonic schizophrenia; and residual schizophrenia.

In some embodiments, the compositions and methods of treatments disclosed herein are useful in the treatment of a negative symptom of schizophrenia.

In some embodiments, the compositions and methods of treatments disclosed herein are useful in the treatment of a positive symptom of schizophrenia.

The duration of treatment according to the method of treating schizophrenia according to the teachings is any suitable duration as determined by a treating health-care professional, typically a psychiatric doctor.

In some embodiments of the method of treating schizophrenia according to the teachings herein, the average daily dose of BCP administered to a human subject is from about 0.4 mg/kg to about 2 mg/kg, such as, for example, from about 0.4 mg/kg to about 1.5 mg/kg, from about 0.4 mg/kg to about 1.8 mg/kg, from about 0.4 mg/kg to about 1.6 mg/kg, from about 0.4 mg/kg to about 1.4 mg/kg, from about 0.4 mg/kg to about 1.2 mg/kg, from about 0.4 mg/kg to about 1 mg/kg, from about 0.4 mg/kg to about 0.8 mg/kg, from about 0.4 mg/kg to about 0.6 mg/kg or from about 0.4 mg/kg to about 0.5 mg/kg.

In some embodiments of the method of treating schizophrenia according to the teachings herein, the average daily dose for a human subject (especially an adult human, weighing between about 40 kg and about 120kg) is in the range of from about 25 mg to about

100 mg, such as about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg.

5 In some embodiments of the method of treating schizophrenia according to the teachings herein, the average daily dose is administered with a frequency of between about once a week to about 3 times per day, for example once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, 6 times per week, once per day, twice per day or 3 times per day.

10 In some embodiments, a composition according to the teachings herein is provided as or made as a dosage form including a plurality of discrete units (e.g., discrete solids or metered liquids), especially discrete solid units such as pills (including tablets and caplets) and capsules (including gelcaps), where each unit includes BCP in the range of from about 25 mg to about 100 mg, such as about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 15 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg. In some such embodiments, such a dosage form is exceptionally useful for the once-daily administration of the desired average daily dosage.

20 According to some embodiments, the composition disclosed herein may be administered by any suitable route of administration, including but not limited to oral administration, parenteral administration (including intravenous injection, intramuscular injection, intradermal injection, intraperitoneal injection, intrathecal injection and subcutaneous injection), and rectal administration. That said, in some embodiments, oral administration is preferred due to the proven oral availability and substantial-non toxicity of BCP.

25 For oral administration, the composition disclosed herein may comprise a pill, a capsule, a dragee, a powder, granules, an ingestible solution (such as a liquid, a gel, a syrup, or a suspension) and the like, for oral ingestion by a subject. In a preferred embodiment, a composition for oral administration comprises a pill or a capsule.

30 In a preferred embodiment, the composition is a gastroresistant orally-administrable dosage form, that is to say, an orally-administrable dosage form configured to carry the BCP through the stomach to be released into contact with the digestive tract only after passage through the duodenum. For example, in some such embodiments, the composition is in the form of a gastroresistant soft gel capsule, comprising between 25 mg and about 100 mg BCP in a carrier comprising vegetable oil. Some embodiments of the method, when implemented

with an adult human subject, comprise orally ingesting a single such capsule twice a day for at least one month, so that the average daily dose is between about 50 mg and about 200 mg BCP.

In some embodiments, the composition described herein further comprises at least one additional antipsychotic agent, such as, for example, a typical antipsychotic agent (including, but not limited to, one or more of chlorpromazine, haloperidol, perphenazine, or fluphenazine), and/or an atypical antipsychotic agent (including, but not limited to, one or more of clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone), or combinations thereof.

In some embodiments of the method of treatment, the BCP is administered together with at least one additional antipsychotic agent, such as, for example, a typical antipsychotic agent (including, but not limited to, one or more of chlorpromazine, haloperidol, perphenazine, or fluphenazine), and/or an atypical antipsychotic agent (including, but not limited to, one or more of clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone), or combinations thereof.

In some embodiments where the BCP and an antipsychotic agent are administered together, BCP and the additional antipsychotic agent are co-administered in a single dosage form.

In some embodiments where the BCP and an antipsychotic agent are administered together, BCP and the additional antipsychotic agent are co-administered in separate dosage forms, either sequentially or simultaneously. For example, the additional antipsychotic agent may be administered prior to administration of BCP, or the additional antipsychotic agent may be administered subsequent to administration of BCP.

Although not wishing to be bound to any one theory, the Inventors consider that it is likely that at least part, if not all, of the herein demonstrated efficacy of BCP in treating schizophrenia relates to the CB2 receptor agonist properties of BCP.

Thus, according to an aspect of some embodiments of the teachings herein, there is provided a composition comprising a CB2 receptor agonist and a pharmaceutically effective carrier for use in treating schizophrenia.

According to an aspect of some embodiments of the teachings herein, there is also provided the use of a CB2 receptor agonist and a pharmaceutically effective carrier in the manufacture of a medicament for treating schizophrenia in a subject in need thereof.

According to an aspect of some embodiments of the teachings herein, there is also provided a method for treating schizophrenia in a subject in need thereof, the method

comprising administering a pharmaceutically-effective amount of a CB2 receptor agonist to the subject.

Exemplary embodiments of the teachings herein are discussed hereinbelow with reference to specific materials, methods and examples. The material, methods and examples discussed herein are illustrative and not intended to be limiting. In some embodiments, methods and materials similar or equivalent to those described herein are used in the practice or testing of embodiments of the invention. It is to be understood that the invention is not necessarily limited in its application to the details of construction and the arrangement of the components and/or methods set forth in the following description and/or illustrated in the drawings. The invention is capable of other embodiments or of being practiced or carried out in various ways.

EXAMPLES

MATERIALS AND METHODS

BCP was obtained from Sigma-Aldrich (St. Louis, MO, USA), catalogue Nr. W225207 and further purified using preparative HPLC (HP1090 series; column, PEGASIL ODS (Senshu Sci. i.d. 10 ×250mm); solvent, 70% CH₃OH; flow rate, 2.0 mL/min; detection, UV 220 nm] to remove other sesquiterpenes. GC-MS analysis showed that the BCP used in the below included 95% E-BCP, 3% Z-BCP, 1% BCP Oxide and traces of alpha humulene. AM630 was obtained from Cayman Chemical Company (Ann Arbor, Michigan, USA). PCP, Cremophor EL and DMSO were obtained from Sigma-Aldrich (St. Louis, MO, USA).

Animal model of schizophrenia:

The mouse model of schizophrenia was established. Phencyclidine (PCP), an NMDA antagonist which induces schizophrenia and psychotic effects in humans, was administered to murine pups (injection of 5mg/kg in saline) on postnatal days 3, 5, 7, 9, 11, 13, and 16. This treatment induces long-lasting schizophrenic-like effects in mice that lasted into adulthood. The therapeutic effects of beta-caryophyllene, a dietary cannabinoid and CB2 receptor agonist, in accordance with the teachings herein were evaluated.

1. TREATMENT OF MICE WITH BCP AT POSTNATAL DAYS 3-16

BCP (final dose 10mg/kg in 1:0.6:18 Cremophor EL:ethanol:saline) was administered by injection 1 hour after PCP. Results were obtained from two different litters, each of which was divided into 3 groups:

Group 1: vehicle (n=6 and 4 pups, respectively);

Group 2: PCP (n=6 and 5 pups, respectively);

Group 3: PCP+BCP (n=5 and 5 pups, respectively).

In Fig 17 BCP (final dose 10mg/kg in 1:0.6:18 Cremophor EL:DMSO:saline) was administered by injection 1 hour after PCP. Results were obtained from one litter which was
5 divided into the three groups.

Assessment of positive/negative schizophrenic-like behavior:

Open-field test (crossing and rearing)

Mice were assessed for hyperactivity behavior on postnatal day 16 (FIG. 2). Mice were
10 placed in the center of a transparent glass cube cage 30 x 40 X31 cm divided into squares of 7.5 x 7.5 cm. The number of squares and rearing activity were counted for 8 min.

Positive symptoms. Prepulse Inhibition (PPI) of the startle reflex

In this experimental model, a weak stimulus (74-90 dB tone) inhibited the subsequent
15 response to a strong stimulus (120 dB tone). Reduced prepulse inhibition of the startle reflex (PPI) was taken as an index of the positive symptoms of schizophrenia (Josselyn and Vaccarino, 1998).

PPI was assessed similarly to the method described by Varty et al. In the employed model, mice were placed in a startle chamber and allowed to acclimate for 5 min. A
20 loudspeaker produced a 65dB background white noise or the various acoustic pre-pulse stimuli (dB): 74, 78, 82, 86, and 90 (20 ms). A 120 dB (40 ms) stimulus was given first to induce a response to startle. The response of the mouse was transduced and stored by a computer. Each test session lasted for 11 min and consisted of 5 presentations of each of the trial types presented in random order and separated by 15 second intervals. The amount of
25 prepulse inhibition was calculated as $\%PPI = [1 - (\text{startle response for prepulse+pulse}) / (\text{startle response for pulse alone})] \times 100$.

Negative symptoms

Anxiety as measured by the paucity of time spent on the two, anxiety-provoking, open
30 arms (as opposed to the two enclosed arms) of an "Elevated Plus Maze" was used as a parameter of negative symptoms of schizophrenia (Josselyn and Vaccarino, 1998). The plus maze was elevated 50 cm above the table top. Behavior of each mouse was recorded for 5 min by a video camera and scored using the "EthoVision" software (Noldus Information Technology, Wageningen, The Netherlands), measuring the number of entries as well as the

amount of time spent in each arm, open or closed. Increased time spent in the closed arms indicated increased anxiety. Increased time spent in the opened arms indicated anxiolytic behavior (reduced stress).

5 RESULTS

Body weight

Body weight was recorded at each day of injection (FIG. 1A). PCP was shown to significantly reduce the body weight. The results show that BCP significantly reversed the inhibitory effect of PCP on body weight ($p < 0.0001$ for PCP+ BCP vs. PCP).

10 It was shown that at PND 7, PCP induced a significant reduction in body weight. BCP reversed the reduction in body weight during the first week of life (FIG. 1B) but, under these conditions (injections in ethanol-based vehicle as described above) did not restore the weight completely. However, when vehicle mixture was changed to DMSO-based, BCP completely reversed the effect of PCP on body weight (FIG 12C).

15 At postnatal day (PND) 17, the difference between vehicle- and PCP-treated groups in body weight was still significant ($p < 0.0001$) (FIG. 2C). There was no significant difference between groups treated with PCP with or without BCP.

Rearing and exploration

20 At PND 17, at the end of treatment with BCP, locomotor activity, hyperactivity, and exploratory behaviors were tested with the open-field test (FIGs 2A, 2B). PCP significantly inhibited both ambulation and rearing behaviors. Treatment with BCP reversed the effects of PCP on rearing and exploration. In addition, it is seen that the effect of BCP is not dependent on ethanol as its solvent. It is seen that a DMSO-based carrier completely reversed the effects
25 of PCP on ambulation (FIG 12A) and rearing behavior (FIG 12B).

Results according to sex

Changes in body weight and results from the open-field test at PND 17 were separated according to the sex of mice (FIGs 3A-F).

30 Females appeared to be more sensitive to the effect of PCP (ambulation $p < 0.006$; $p < 0.03$ rearing). Treatment with BCP reversed a proportion of the effects of PCP on ambulation and rearing behavior of female mice (FIGs. 3E, 3F, respectively) but not the effect of PCP on body weight (FIG. 3D). Locomotor activity of male mice appeared to be less sensitive to the treatment of PCP or PCP+BCP (FIGs. 3A-3C). However, the effect of BCP on

PCP-induced reduction of body weight in male mice appeared to be more prominent (FIG 3A).

These results suggest that in some embodiments the administration of BCP for the treatment of schizophrenia has a different effect on male and female mice, being more effective in the treatment of female mice.

Mice were re-evaluated in the open-field test at PND 35-37. Results of body weight, rearing and ambulation were separated according to the sex of mice (FIGs. 4A-F).

Treatment with BCP significantly reversed the effect of PCP on female body weight (FIG. 4D). At this age there was no significant difference in male body weight between the groups (FIG. 4A).

In males, treatment with BCP significantly reduced rearing behavior as compared to vehicle and PCP-treated groups (FIG. 4B).

In males, treatment with PCP significantly increased the locomotor activity compared with vehicle treatment, while administration of BCP reduced locomotor activity (FIG. 4C).

In females, no differences in rearing and exploration behaviors were seen between the different groups (FIGs. 4E, 4F, respectively).

It was concluded that treatment with BCP significantly reversed the effect of PCP in males.

20 Prepulse inhibition testing

Mice were tested at age 8 weeks in the Pre-Pulse Inhibition test (FIGs. 5A-D).

Response to startle

The response to startle stimuli was not significantly different between groups (in males (FIG 5A) or in females (FIG 5C)). It was concluded that mice in all groups had no problem in hearing and were not apathetic.

% Inhibition

Males treated with PCP showed a significant reduction in their ability to adjust to sound stimulus as compared to vehicle treated mice. BCP reversed this effect (FIG. 5B).

No significant difference in the ability to adjust to sound stimulus was seen in females for the PCP-treated group or PCP+BCP treated group (FIG. 5D).

It was concluded that treatment with BCP significantly reversed the effect of PCP on the sensorimotor-gate in males.

Elevated-Plus Maze test

At age 13 weeks old, mice were tested in the Elevated-Plus Maze test which indicates the level of anxiety (FIGs. 6A-H).

Phencyclidine alters the level of anxiety. However its effect is dependent on the strain
5 of mice, sex and possibly age (Turgeon, 2011; Wily, 1995).

There was no significant change in the time spent in the closed arm or open arm (all length of arm), for either females or males (FIGs. 6A, 6B, 6C, 6D, respectively).

PCP reduced the time spent in the distal end of the opened arm (the very far end of the arm from the center) for females, and BCP reversed this effect (FIGs 6E, 6G). In FIGs 6F, 6H,
10 PCP increased the time spent in the distal end of the opened arm (the very far end of the arm from the center) for males, and BCP reversed this effect.

It was concluded that PCP induced anxiety in female mice and anxiolytic effect in male mice. BCP reversed both effects.

15 Expression level of CB1 and CB2 receptor in mice at 9 days old (mRNA) or 2 weeks old (protein)

Brain tissue of control mice (saline treated) and mice treated with PCP were analyzed in the left and right cortex and brain stem (FIGs. 7A-I; FIG 8. Results from the cortex and brain stem were reported by the Inventors in 2011 (Anavi-Goffer et al).

20 No difference in GAPDH was seen in the left cortex, right cortex or brain stem (FIGs. 7A-7C, respectively).

No significant increase in mRNA expression of CB1 receptor was found in the left or right cortex of the PCP-treated mice (FIGs. 7D, 7E, respectively). A significant increase in mRNA expression of CB1 receptor was found in the brain stem of the PCP-treated mice
25 (FIG. 7F).

A significant increase in mRNA expression of CB2 receptor was found in the left cortex of the PCP-treated mice (FIG. 7G) but in the right cortex there was no difference between control and PCP-treated mice (FIG. 7H). A significant increase in mRNA expression of CB2 receptor was found in the brain stem of the PCP-treated mice (FIG. 7I).

30 It is noteworthy that these results are the opposite of the observed in Western blotting, (FIG. 8) being about 50 kDa (the predicted molecular weight of the CB2 receptor) but in line with these at 64 kDa, suggesting that the CB2 receptor may form a complex with another protein X. This suggests that the change in cannabinoid receptor expression is specific (as no change was found for GAPDH or actin). This also suggests a malfunction in the regulation of

cannabinoid receptor synthesis, leading to the accumulation of cannabinoid receptor mRNA in the left cortex and brain stem. On the other hand, synthesis in the right cortex appeared to lead to the formation of CB2 receptor-protein X complexes.

5 Expression level of GAD67 in mice at 9 days old (mRNA) or 2 weeks old (protein)

Brain tissue of control mice and mice treated with PCP were analyzed for GAD67, a neurochemical marker for schizophrenia (FIG. 9A-F). In the left cortex, GAD67 protein level was significantly decreased (FIG. 9A) but no change was found at the mRNA level FIG. 9D). In the right cortex, the reduction in protein level of GAD67 did not reach a significant level
10 and no change was seen in the mRNA level (FIG. 9B, FIG. 9E). In the brain stem, GAD67 mRNA level was increased in the PCP-treated group (FIG. 9F), although the results of Western blotting showed a non-significant reduction in GAD67 protein level (FIG. 9C). This suggests that there might be a common mechanism which links the changes in GAD67 to those of CB1 and CB2, and this mechanism may be related to the function of GABAergic
15 neurons.

Expression of MGL in 2 week old mice

Brain tissues were analyzed for MGL, an enzyme which degrades 2-AG an endocannabinoid (FIGs. 10A-C, FIG 11B) in control mice and mice treated with PCP. mRNA
20 levels of MGL decreased in the left cortex of the PCP-treated group (FIG. 10A), but not in the right cortex (FIG. 10B). The direction of these results was correlated with the reduction in protein level of MGL as analyzed with Western blotting (FIG. 10C).

A scheme of synthesis and degradative enzymes of the endocannabinoid system is shown in FIG. 11A (FIG 11A and 11B were published by Anavi-Goffer & Mulder,
25 Chembiochem. 2009 10:1591-8).

II. POSTNATAL INDUCTION OF SCHIZOPHRENIA (DAYS 3-15) FOLLOWED BY TREATMENT OF ADOLESCENT MICE WITH BCP (POSTNATAL DAYS 43-61)

METHODS

30 PCP 5mg/kg was administered by injection on PND 3, 5, 7, 10, 12, 13, 15 and 17. Body weight was measured at every injection between PND 3-17. The open field test was conducted on PND 16.

When the mice were adolescent (PND 43-61), BCP (5 mg/kg in a mixture of DMSO:Cremophor EL:saline 0.6:1:18.4) was injected twice a week (on Sunday and

Wednesday) for 3 weeks, a total of 6 injections. After the final BCP injection, mice were tested in the open field test (PND 63), Elevated Plus Maze test (PND 64), PPI test (PND 68) and behavior at the Phenotyper cage (PND 91). Mice were re-tested at adulthood on PND 104 (open field), PND 105 (Phenotyper) PND 106 (PPI).

5

RESULTS

Body weight

As seen in FIG. 13A, PCP significantly reduced body weight in male and female mice as measured on days 3, 5, 7, 10, 12, 15 and 17.

10 Injections of BCP (5 mg /kg) on PND 43-61 did not affect body weight (FIG. 14A). At age PND 63 there was no significant difference in the body weight between vehicle-treated mice and PCP-treated mice (FIG. 14B).

Ambulation, rearing

15 At PND 16, PCP significantly inhibited ambulation, rearing behaviors (FIGs. 13B, 13C).

BCP treatment during adolescence significantly reversed the effect of PCP on ambulation in male and female mice at PND 63 (FIGs. 14C-14E). BCP treatment in adolescence significantly inhibited the exploration of mice compared with saline-treated
20 mice. BCP reversed the effect of PCP on rearing in both females and males (FIGs. 15A-15C).

On PND 104 a relapse in exploratory behavior was evident in the schizophrenic female mice that had been treated with BCP (last BCP treatment was on PND 61), as seen in FIGs 23A, 23C. Rearing behavior of male PCP-treated mice that had been treated with BCP was still significantly higher than that of PCP-treated mice with no BCP treatment (FIGs 24B,
25 24C). There was no difference in body weight between groups (FIG. 24E). BCP treatment did not increase body weight in females and males, rather reduced body weight of PCP+BCP treated group (vehicle vs. PCP+BCP, $P=0.06$).

BCP treatment in adolescence did not reverse the effect of PCP on self-grooming (total, without stimuli) in females or males at PND 104 (FIGs 24A, 24B, 24C).

30

Prepulse inhibition and startle response

BCP treatment in adolescence significantly reversed the effect of PCP on pre-pulse inhibition (FIG. 16A). BCP had no substantial effect on saline-treated mice. BCP treatment at adolescent significantly reversed the effect of PCP on startle response in females (FIG. 16B).

In males, there was no difference in the response to the startle stimuli between groups (FIG. 16C).

BCP treatment at adolescence significantly reversed the effect of PCP on response to pre-pulse tones (FIGs. 17A-17C). BCP had no effect on saline-treated mice.

5 There was no difference between groups in the response to the startle stimuli at the end of the PPI test (FIGs. 18A-18C). BCP treatment at adolescence did not affect the response to startle at the end of the PPI test (FIGs. 18A-18C).

At PND 106, there was no difference in the response to the startle stimuli (120 dB) between groups (FIGs. 25A-25C). BCP reversed the effect of PCP on the response to tones
10 (FIGs. 25D-25F). BCP treatment at adolescence reversed the effect of PCP on the % pre-pulse inhibition (PPI) (FIGs. 25G-25I).

Plus-Maze Test

BCP treatment at adolescence did not reverse the effects of PCP on behavior in the
15 Plus Maze test at age 64 days (6 weeks) (FIGs. 19A-19F).

PhenoTyper test

At PND 91, PCP increased the time spend at the Hidden Zone, indicating the PCP-treated mice had higher level of anxiety of mice at the PhenoTyper cage compared with
20 vehicle-treated mice. BCP treatment at adolescence reversed the effects of PCP on the time spend in the Hidden Zone of PhenoTyper cage in females and males, respectively (FIGs. 20A, 20B). FIG. 20C shows combined results, suggesting that BCP reversed the effect of PCP on anxiety level. PCP appeared to reduce the frequency of entries to the Hidden Zone in males (FIG. 20D) but not in females (FIG. 20E). BCP reversed the effect of PCP in males
25 (FIG. 20D).

PCP reduced the frequency of entries to the wheel. BCP treatment at adolescence reversed the effects of PCP on the frequency of entries to the wheel in the PhenoTyper cage both in females and males (FIGs. 21A, 21B). FIGs. 21C, shows combined results of both sex. These results indicate that BCP reversed the action of PCP on loco/motor behavior.

30 BCP treatment at adolescence did not affect the time spend in the food zone (FIGs. 22A, 22B, 22C).

Compared with PCP-treated group, BCP treatment at adolescence appeared to reduce the time spend at the drinking zone (FIGs. 22D, 22E, 22F).

At PND 105, PCP increased the frequency of entries to the Hidden Zone, indicating an increased level of anxiety.

BCP treatment at adolescence reversed the effects of PCP on the frequency of entries to the hidden zone (FIGs. 26A, 26B, 26C). These results suggest that treatment with BCP reduced the level of stress and anxiety. BCP treatment appeared to reduce the effect of PCP on the frequency of entries to the Wheel Zone FIG. 26. This effect was prominent in males than in females (FIGs. 26D, 26E).

At PND 105, BCP treatment at adolescence reversed the effects of PCP on the time spend at the hidden zone (FIGs. 27A, 27B). These results suggest that treatment with BCP reduced the level of stress and anxiety. BCP treatment at adolescence showed a trend to reverse the effect of PCP on the time spend in the wheel (FIGs. 27C, 27D, 27E).

III. EFFECTS OF AM630 (6-iodopravadoline)

AM630 (6-Iodopravadoline, CAS 164178-33-0) is a molecule that acts as a potent and selective inverse agonist for the cannabinoid receptor CB2, with a K_i of 32.1 nM at CB2 and 165x selectivity over CB1, at which it acted as a weak partial agonist. It is used in the study of CB2 mediated responses.

MATERIALS AND METHODS

Murine model of schizophrenia: Mice were injected with PCP (5mg/kg in saline) at postnatal days PND 4, 6, 8, 11, 13, 15, and 18 to provide a murine model of schizophrenia. A control group was injected with vehicle (0.6:1:18.4 DMSO:Cremophor EL:saline) alone. Each experiment was repeated twice. In each experiment, male mice were divided into 4 groups:

- Group 1: vehicle (n=4 pups, 1+3 pups, respectively);
- Group 2: PCP (n=5 pups, 2+3 pups, respectively);
- Group 3: PCP+BCP (n=6 pups, 2+4, respectively); and
- Group 4:PCP+BCP+AM630 (n=3 pups, 1+2 respectively).

Administration of BCP or BCP+AM630

The effect of co-administering AM630 with BCP was studied.

One hour after each injection with PCP, mice were injected with vehicle or BCP (final dose 10mg/kg in 1:0.6:18 Cremophor EL:DMSO:saline) or BCP+AM630 (equal parts of 20

mg/kg BCP in DMSO and 20 mg/kg AM630 in DMSO, providing a final concentration of 10 mg/kg each of BCP and AM630, mixed together).

RESULTS

5 Rearing and exploration

At PND 17, locomotor activity, hyperactivity, exploratory and grooming behaviors were tested with the open-field test (FIGs 29A and 29B). PCP significantly inhibited both ambulation and rearing behaviors. Treatment with BCP reversed the effects of PCP on rearing and exploration. AM630 reversed the effects of BCP on ambulation and rearing behaviors.

- 10 The behaviors of mice that had been treated with AM630 were not significantly different from these of PCP-treated mice.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single
15 embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

- 20 Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the scope of the appended claims.

- 25 Citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the invention.

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CLAIMS

1. A composition comprising beta-caryophyllene (BCP) and a pharmaceutically effective carrier for use in treating schizophrenia.
2. The composition of claim 1, wherein said schizophrenia is selected from the group consisting of paranoid schizophrenia; disorganized schizophrenia; undifferentiated schizophrenia; catatonic schizophrenia; and residual schizophrenia.
3. The composition of any of claims 1 to 2, wherein said treating comprises treating at least one symptom of schizophrenia selected from the group consisting of a negative symptom of schizophrenia and a positive symptom of schizophrenia.
4. The composition of any of claims 1 to 3, wherein said pharmaceutically effective carrier comprises dimethyl sulfoxide (DMSO).
5. The composition of any of claims 1 to 4, a single discrete unit of the composition comprises BCP at a weight in the range of from about 25 to about 100 mg.
6. The composition of any of claims 1 to 5, formulated as an injectable solution dosage form.
7. The composition of any one of claims 1 to 5, wherein the composition is formulated as an orally-administrable dosage form.
8. The composition of any of claims 1 to 7, further comprising at least one additional antipsychotic agent.
9. The composition of claim 8, wherein said at least one additional antipsychotic agent is selected from the group consisting of chlorpromazine, haloperidol, perphenazine, fluphenazine, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone, or combinations thereof.
10. Use of beta-caryophyllene (BCP) and a pharmaceutically effective carrier in the manufacture of a composition for treating schizophrenia in a subject in need thereof.

11. The use according to claim 10, wherein said schizophrenia is selected from the group consisting of paranoid schizophrenia; disorganized schizophrenia; undifferentiated schizophrenia; catatonic schizophrenia; and residual schizophrenia.
12. The use according to any of claims 10 to 11, wherein said treating comprises treating at least one symptom of schizophrenia selected from the group consisting of a negative symptom of schizophrenia and a positive symptom of schizophrenia.
13. The use of any of claims 10 to 12, wherein said pharmaceutically effective carrier comprises dimethyl sulfoxide (DMSO).
14. The use according to any of claims 10 to 13, wherein a single discrete unit of said composition comprises BCP at a weight in the range of from about 25 to about 100 mg.
15. The use according to any of claims 10 to 14, wherein said composition is made as an injectable solution dosage form.
16. The use according to any of claims 10 to 14, wherein said composition is made as an orally administrable dosage form.
17. The use according to any of claims 10 to 16, wherein said composition further comprises at least one additional antipsychotic agent.
18. The use according to claim 17, wherein said at least one additional antipsychotic agent is selected from the group consisting of chlorpromazine, haloperidol, perphenazine, fluphenazine, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone, or combinations thereof.
19. A method for treating schizophrenia in a subject in need thereof, the method comprising administering a therapeutic composition comprising beta-caryophyllene (BCP) and a pharmaceutically effective carrier.

20. The method of claim 19, wherein said schizophrenia is selected from the group consisting of paranoid schizophrenia; disorganized schizophrenia; undifferentiated schizophrenia; catatonic schizophrenia; and residual schizophrenia.
21. The method of any of claims 19 to 20, wherein said treating comprises treating at least one symptom of schizophrenia selected from the group consisting of a negative symptom of schizophrenia and a positive symptom of schizophrenia.
22. The method of any of claims 19 to 21, wherein an average daily amount of said BCP administered is from about 0.4 mg/kg to about 2 mg/kg.
23. The method of any of claims 19 to 22, wherein said pharmaceutically effective carrier comprises dimethyl sulfoxide (DMSO).
24. The method of any of claims 19 to 23, wherein said administering comprises injecting said composition to said subject.
25. The method of any of claims 19 to 23, wherein said administering comprises orally administering said composition to said subject.
26. The method of any of claims 19 to 25, further comprising co-administering at least one additional antipsychotic agent.
27. The method of claim 26, wherein said at least one additional antipsychotic agent is selected from the group consisting of chlorpromazine, haloperidol, perphenazine, fluphenazine, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone, or combinations thereof.
28. The method of any of claims 26 to 27, wherein said at least one additional antipsychotic agent is co-administered in a single dosage form together with said BCP.
29. The method of any of claims 26 to 27, wherein said at least one additional antipsychotic agent is co-administered in a dosage form separate from said BCP.

30. A composition comprising a CB2 receptor agonist and a pharmaceutically effective carrier for use in treating schizophrenia.
31. Use of a composition comprising a CB2 receptor agonist and a pharmaceutically effective carrier in the manufacture of a composition for treating schizophrenia in a subject in need thereof.
32. A method for the treating schizophrenia in a subject in need thereof, the method comprising administering a therapeutic composition comprising a CB2 receptor agonist and a pharmaceutically effective carrier.

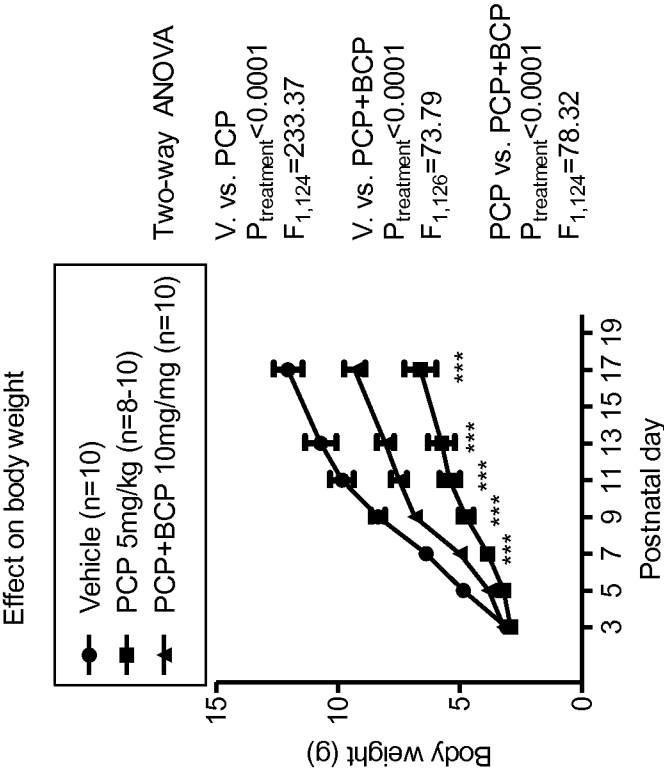


Figure 1A

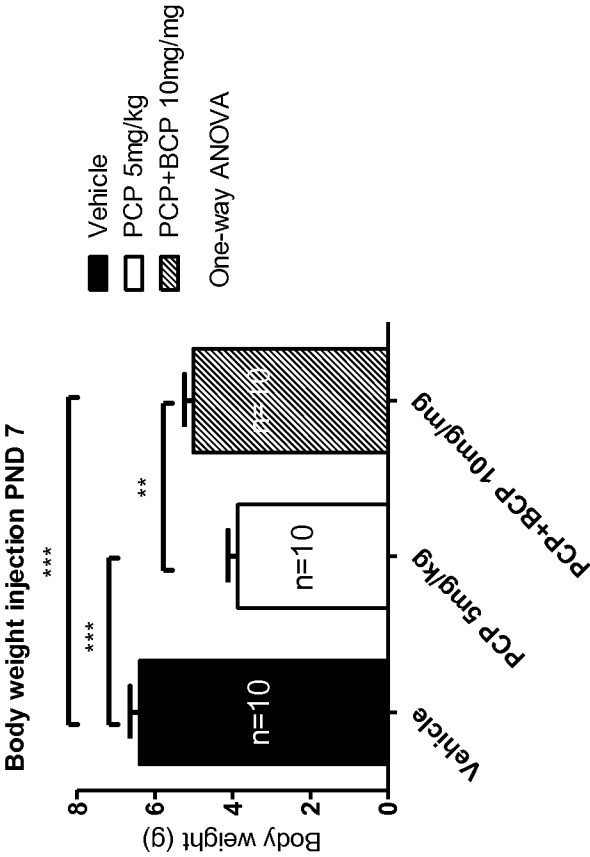


Figure 1B

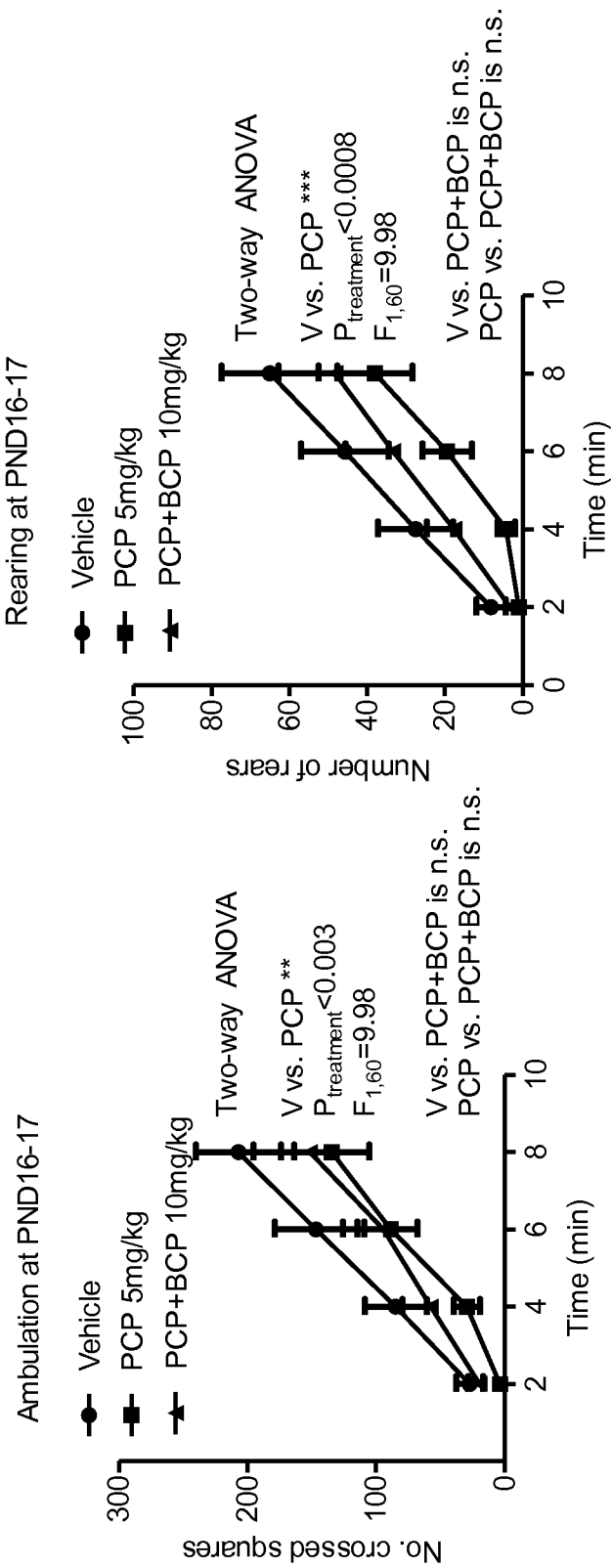


Figure 2A

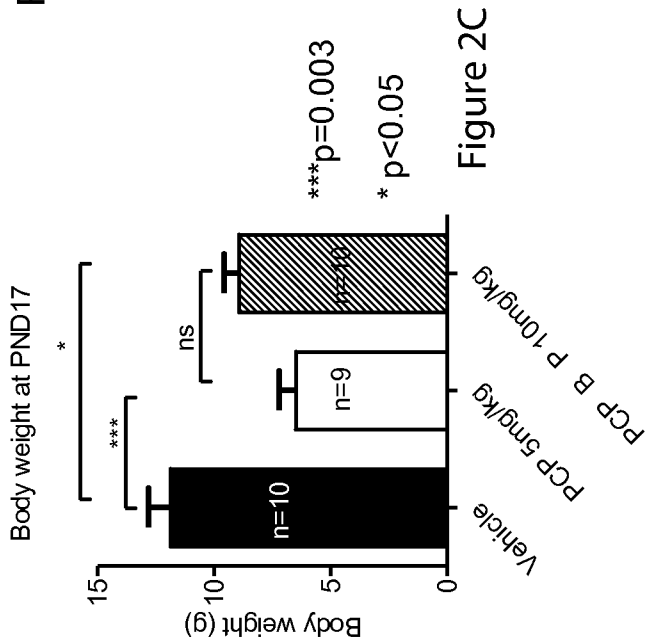


Figure 2B

Figure 2C

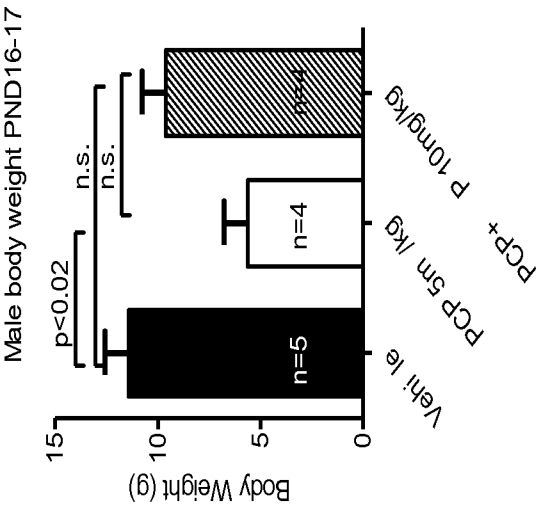


Figure 3A

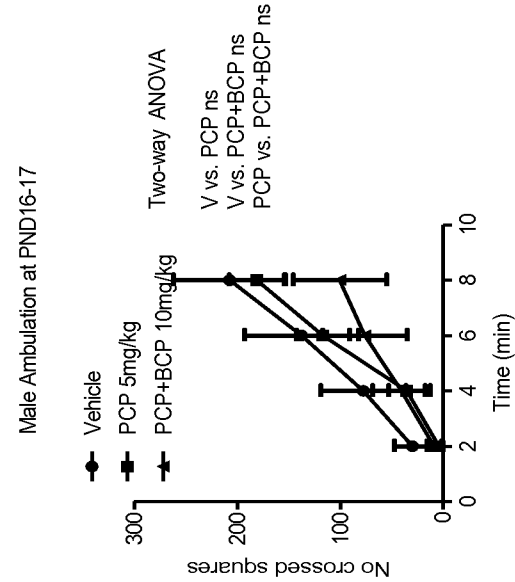


Figure 3B

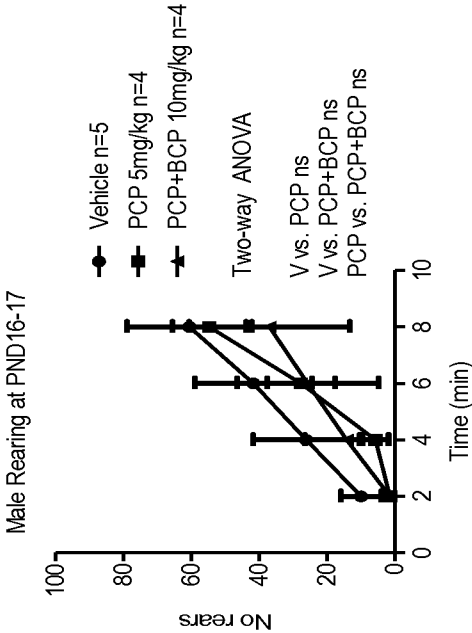


Figure 3C

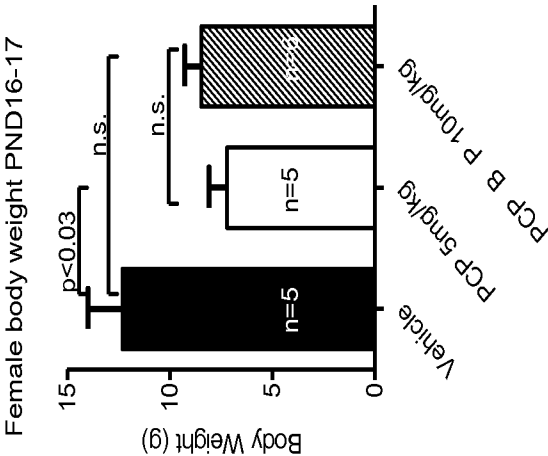


Figure 3D

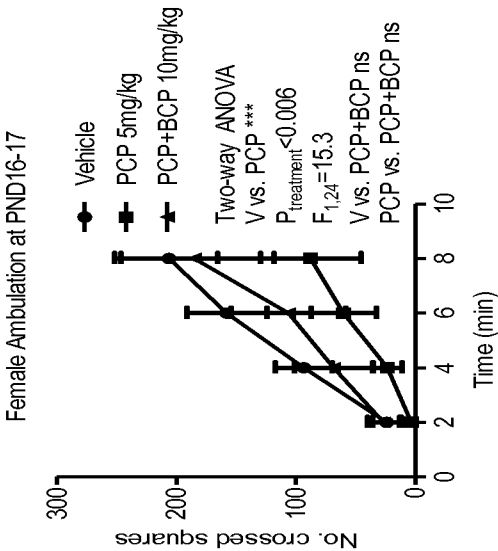


Figure 3E

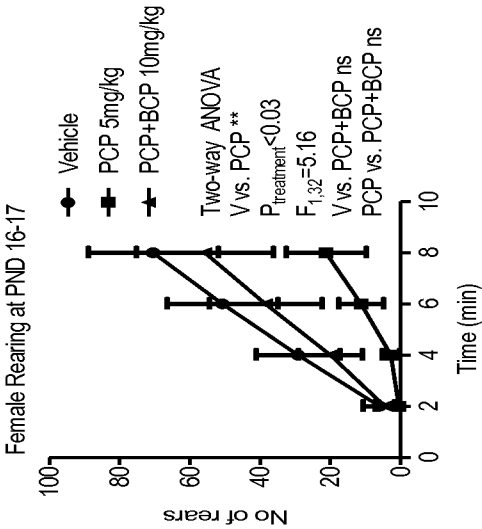


Figure 3F

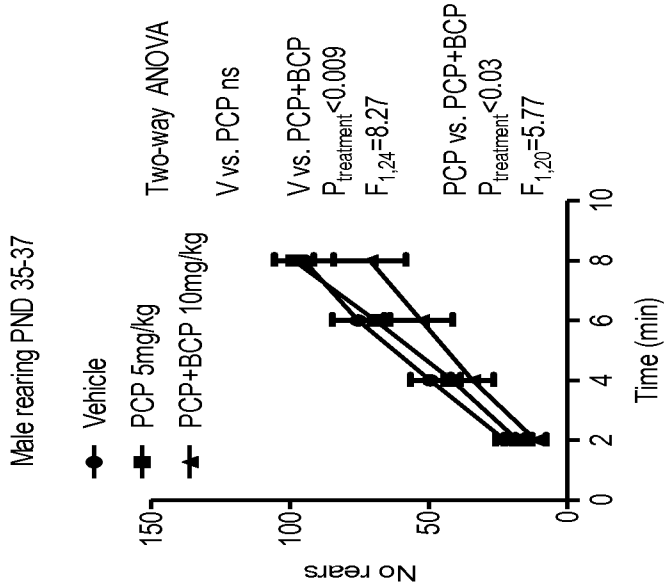


Figure 4B

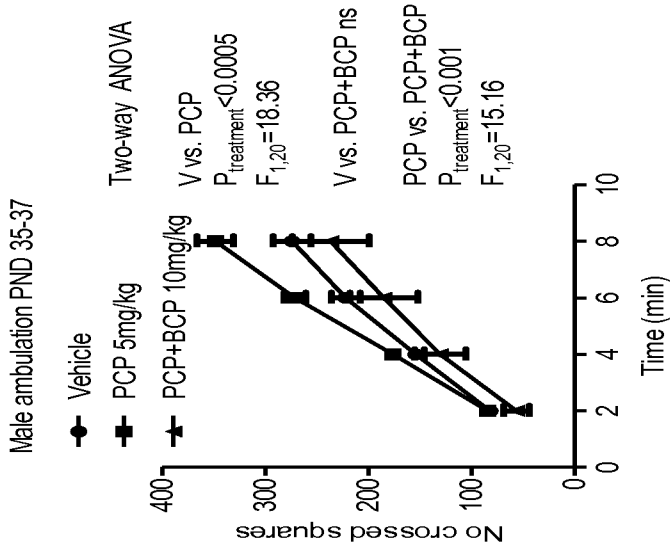


Figure 4C

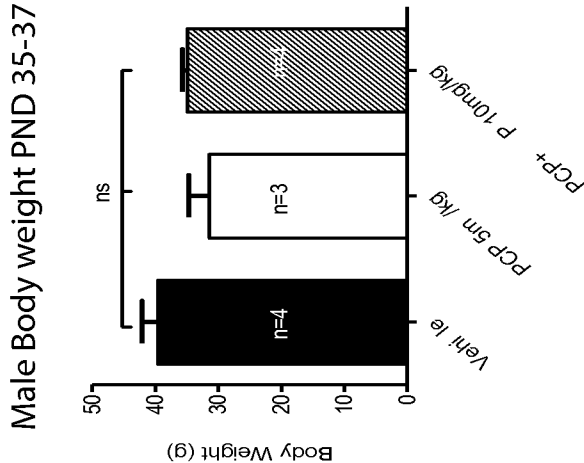


Figure 4A

Female body weight PND 35-37

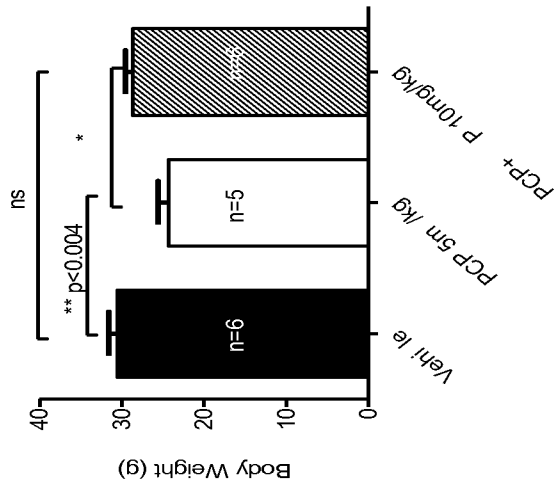


Figure 4D

Female rearing PND 35-37

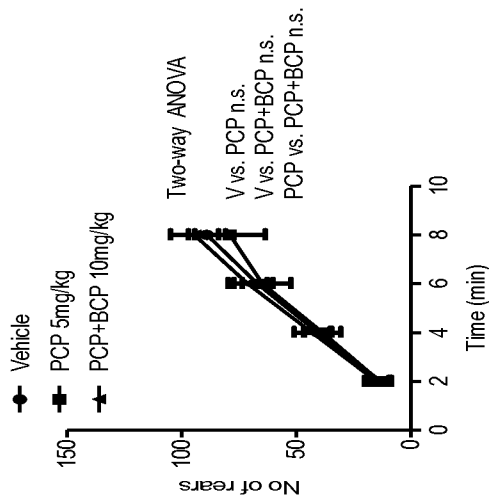


Figure 4E

Female ambulation PND 35-37

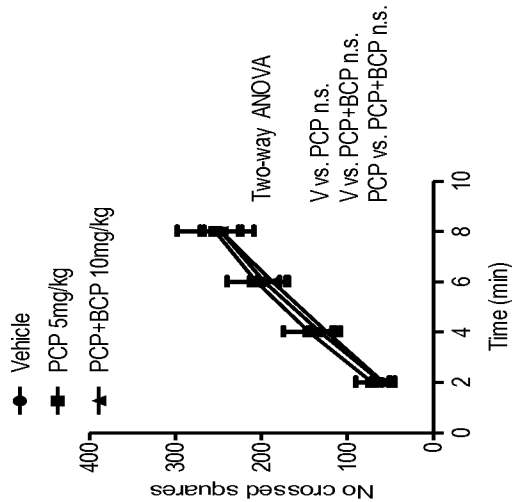


Figure 4F

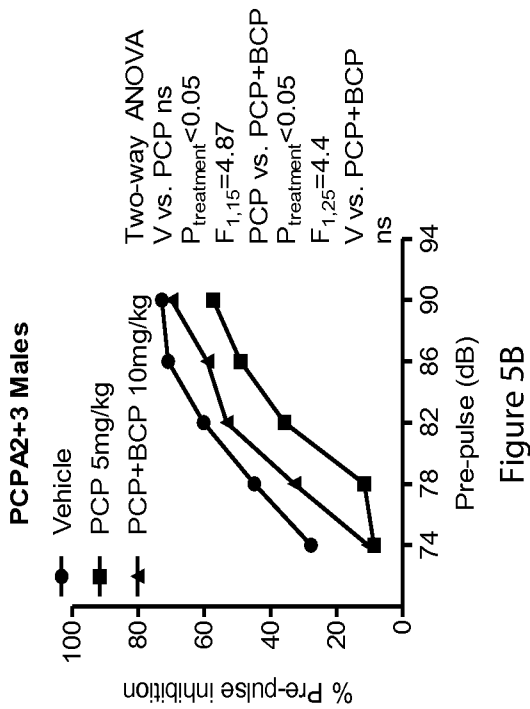


Figure 5B

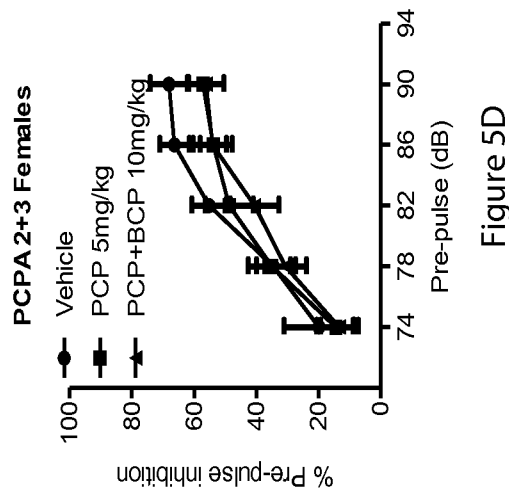


Figure 5D

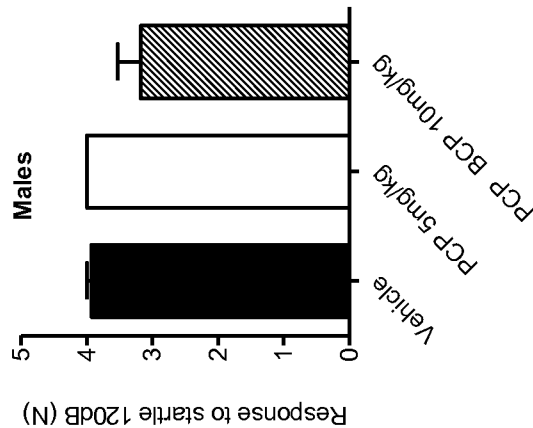


Figure 5A

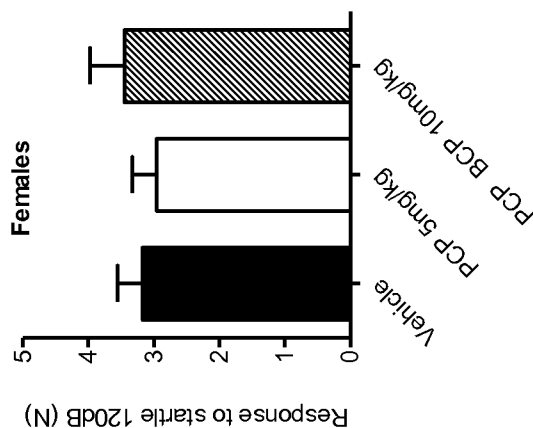
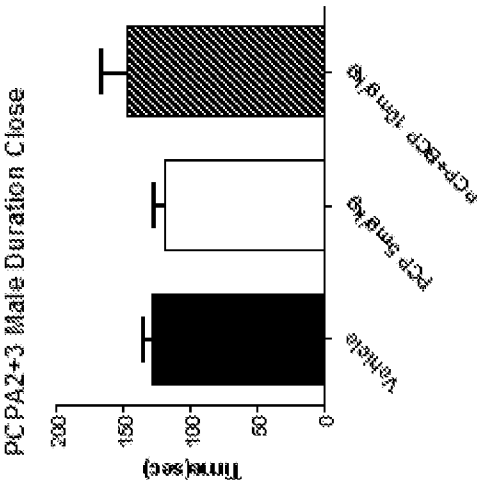


Figure 5C

Figure 6B



PCPA2+3 Male Duration Open

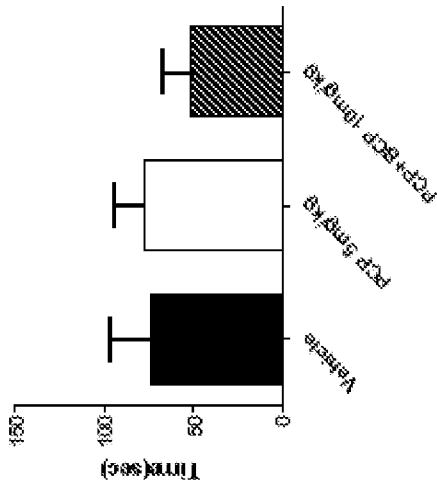
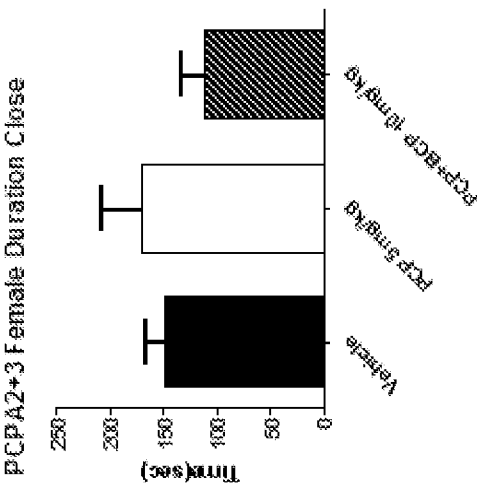


Figure 6D

Figure 6A



PCPA2+3 Female Duration Open

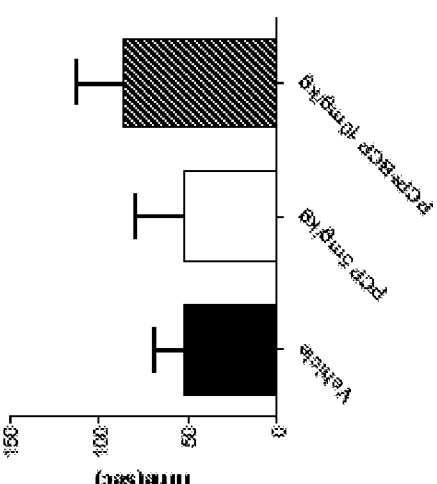
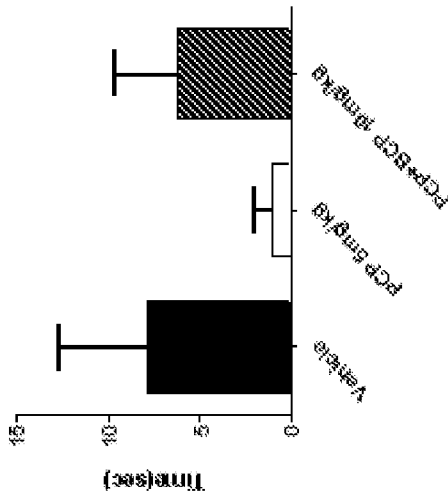


Figure 6C

Figure 6E

PCPA2+3 Female Duration Distal Open



PCPA2+3 female Open distal/Close Duration

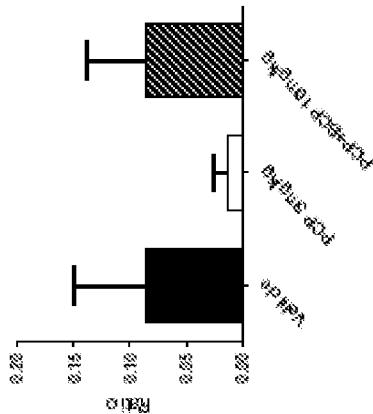
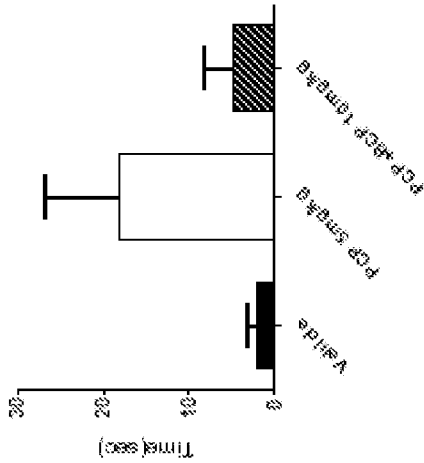


Figure 6G

Figure 6F

PCPA2+3 Male Duration Distal Open



PCPA2+3 Male Open/Close Duration

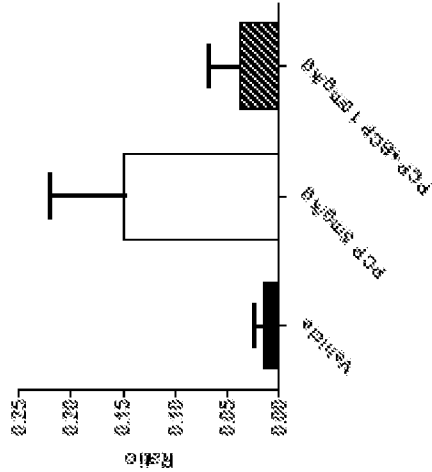


Figure 6H

GAPDH

Left Cortex

Right Cortex

Brain stem

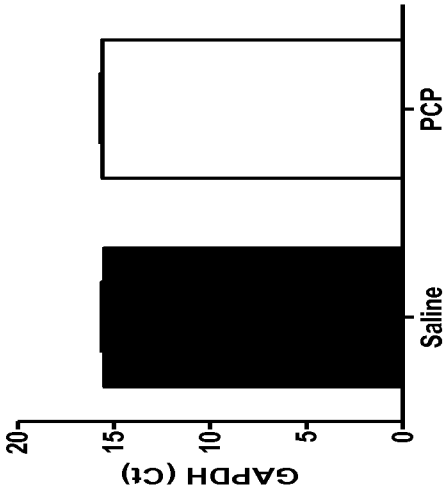


Figure 7A

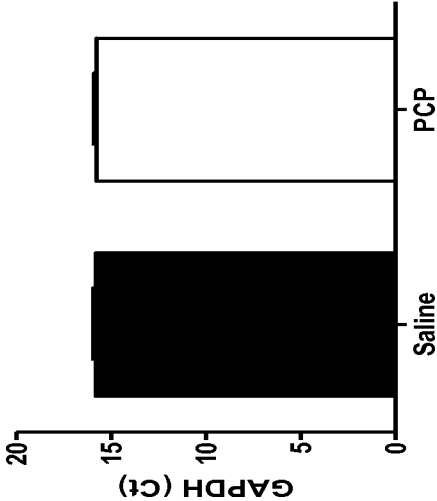


Figure 7B

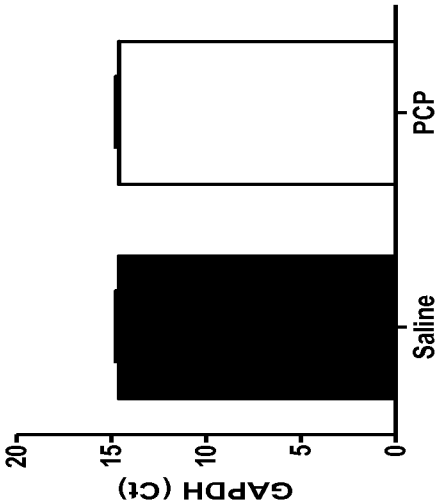


Figure 7C

CB1

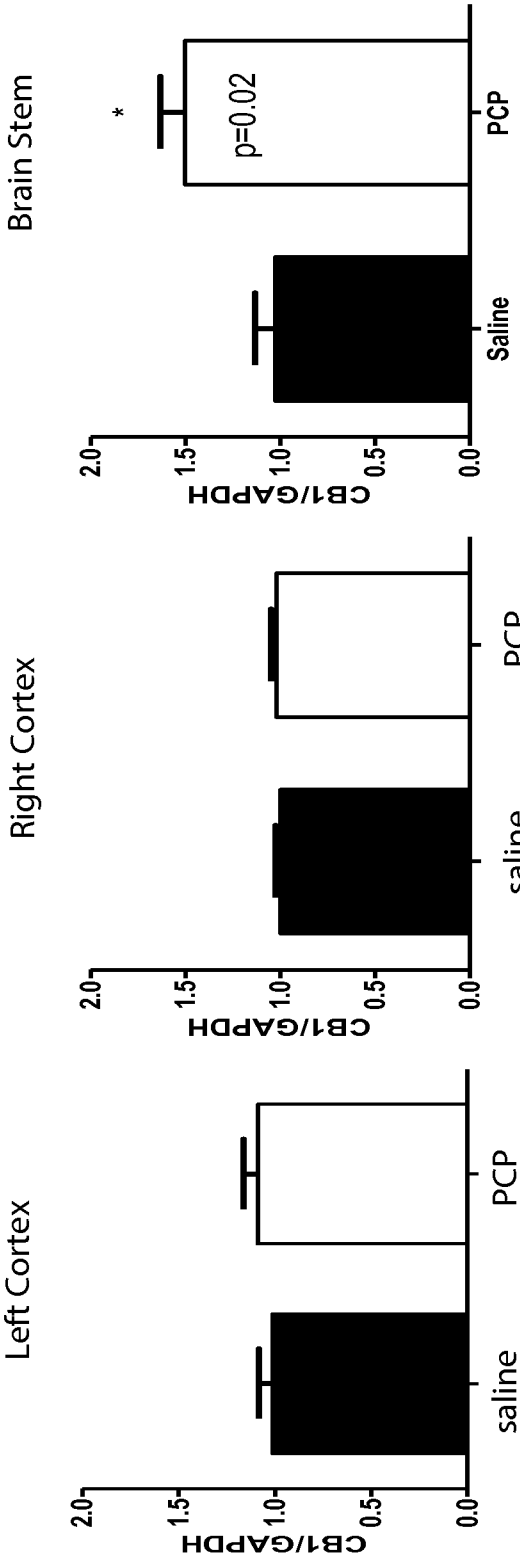


Figure 7D

Figure 7E

Figure 7F

CB2

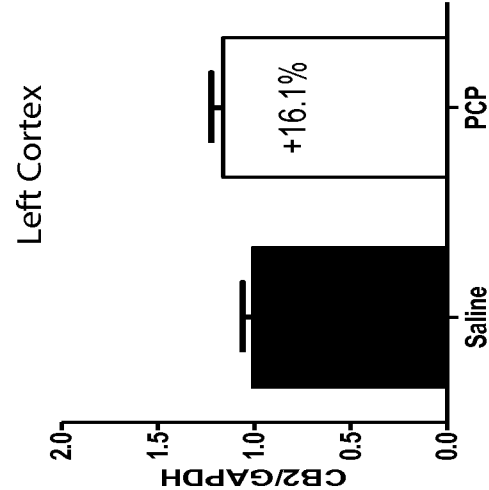


Figure 7G

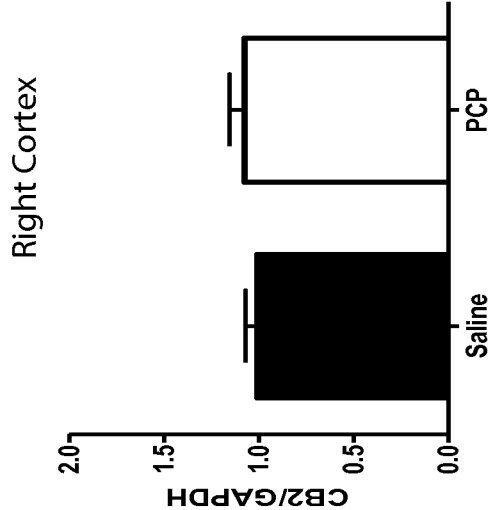


Figure 7H

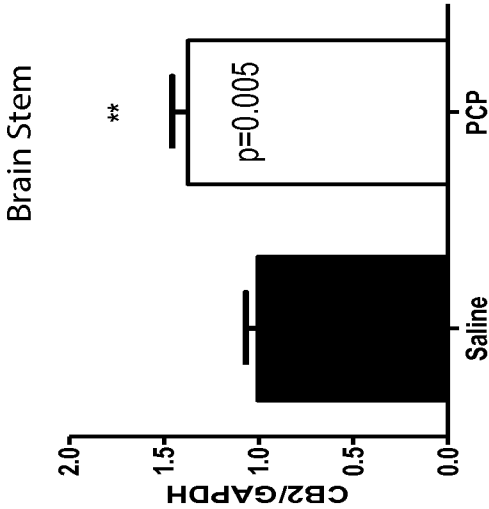


Figure 7I

(-) A reduction in expression in PCP-treated mice compared with control (vehicle-treated) animals.

(+) An increase in expression in PCP-treated mice compared with control (vehicle-treated) animals.

	Left cortex	Right cortex	Basal ganglia	Brain stem
CB1	-17%	ns	-36% p=0.07	-32% p<0.001
CB2 ~50kDa	-17%	ns	-14%	-23% p<0.05
'CB2 complexes' 64 kDa	Signal too low to detect	+87% p<0.001	+74%	-23% p=0.051

Figure 8

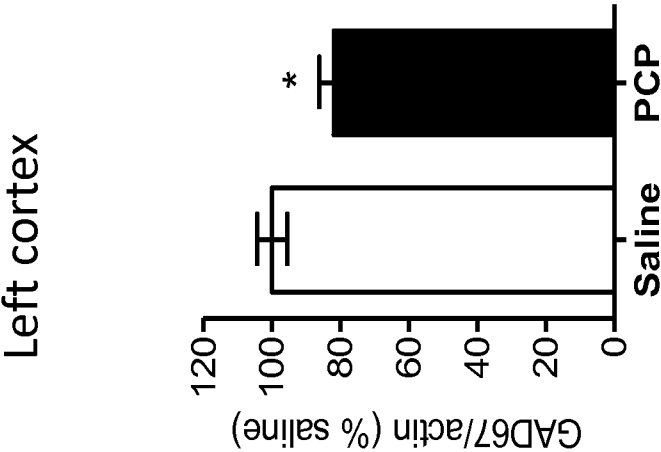


Figure 9A

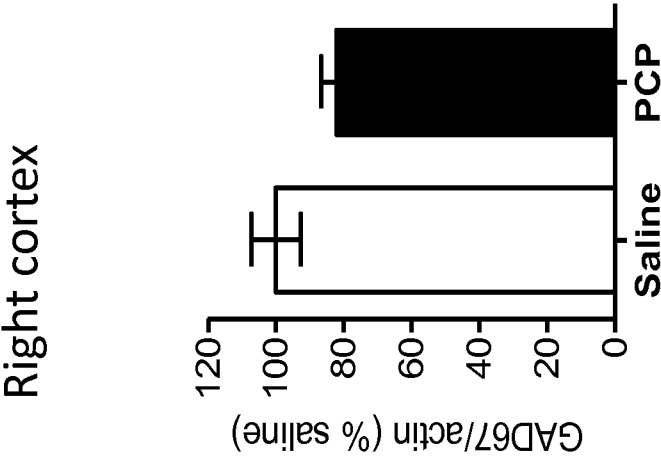


Figure 9B

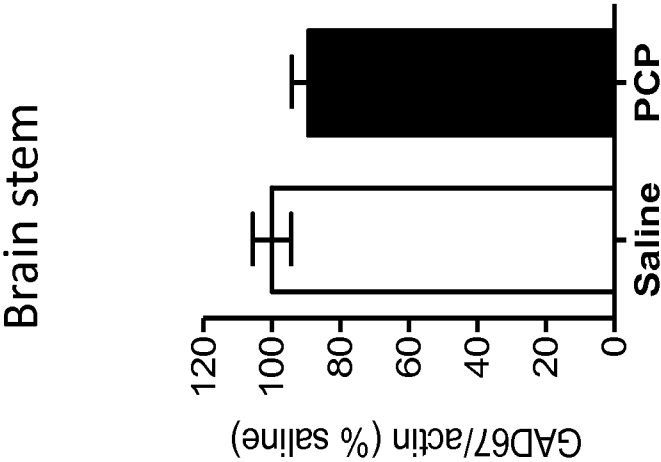


Figure 9C

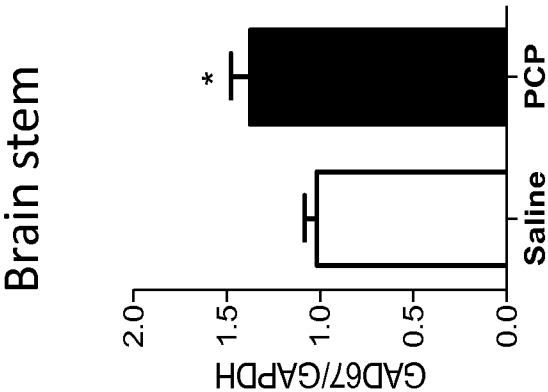


Figure 9F

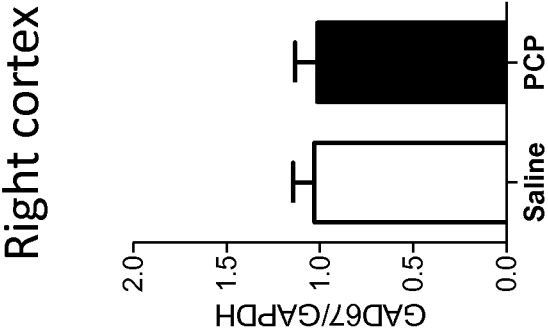


Figure 9E

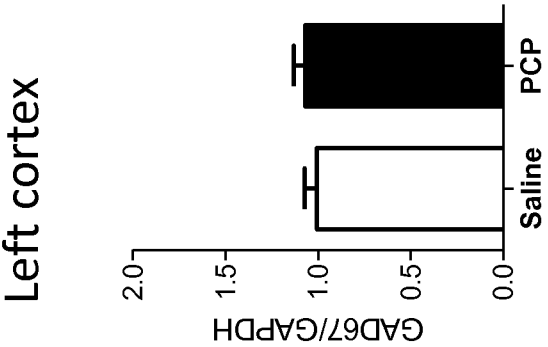


Figure 9D

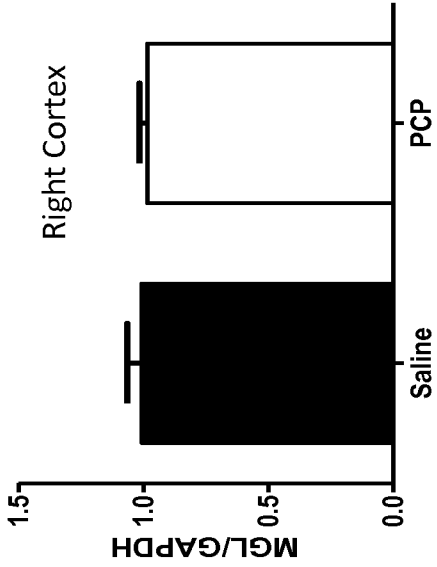


Figure 10B

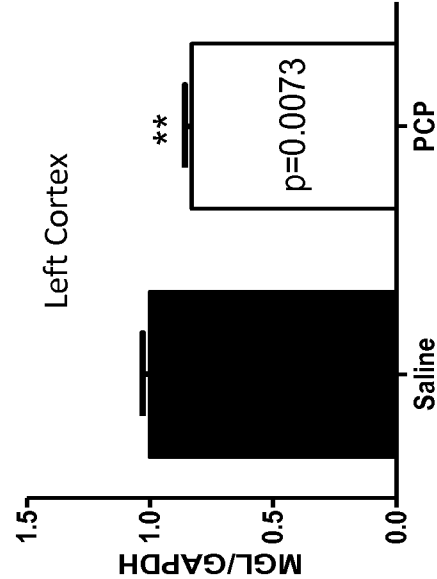


Figure 10A

mRNA MGL

Western blot	Mw	cortex	PCP vs. vehicle
	30 kDa	(-)6.978 ± 3.030	p=0.042 *
	33 kDa	-)13.67 ± 3.821	p=0.004 **
	60 kDa	(-)22.79 ± 5.457	p=0.001 **

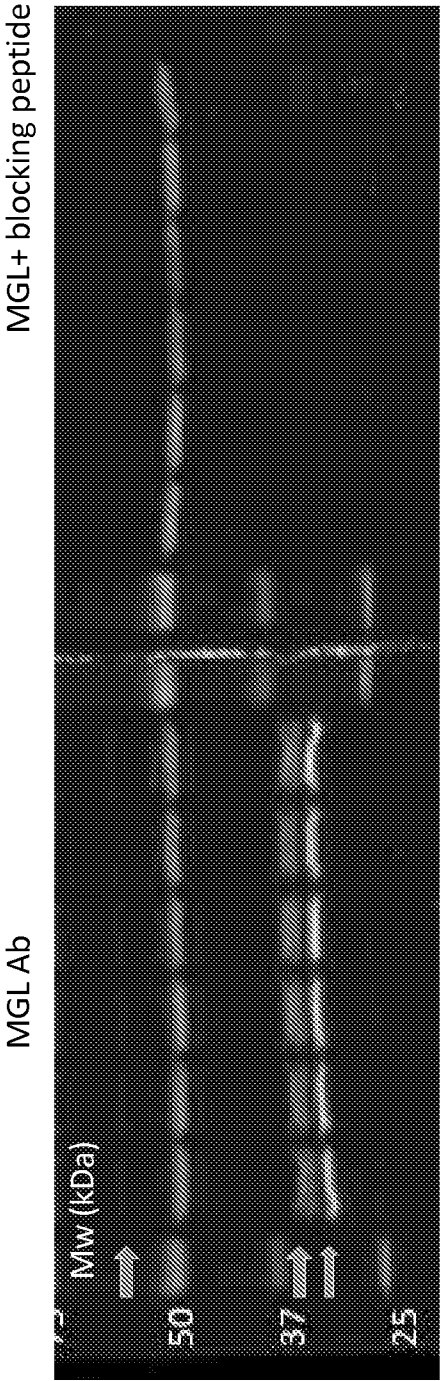


Figure 10C

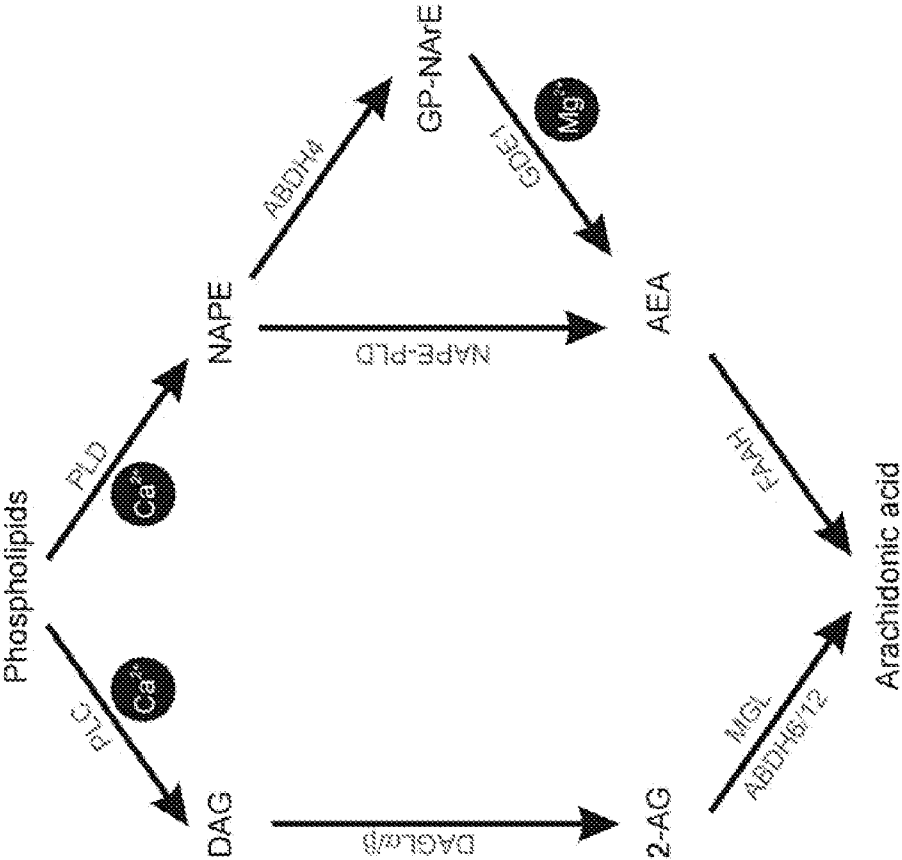


Figure 11A

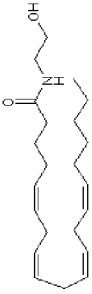
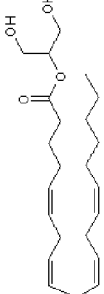
	Ligand	Affinity (K _i , nM)			Efficacy (E _{max} , %)			Potency (EC ₅₀ , nM)		
		CB ₁	CB ₂	Selectivity	CB ₁	CB ₂	GPR55	CB ₁	CB ₂	GPR55
Endocannabinoids										
	Anandamide	90-543	370-2000	3	30-100/ 66	38-64/ 58	73	80-200/30	>1000/ 27	18
	2-AG	58-470	145-1400	3	80/ 92	60/ 87	99	430/520	780/ 620	3

Figure 11B

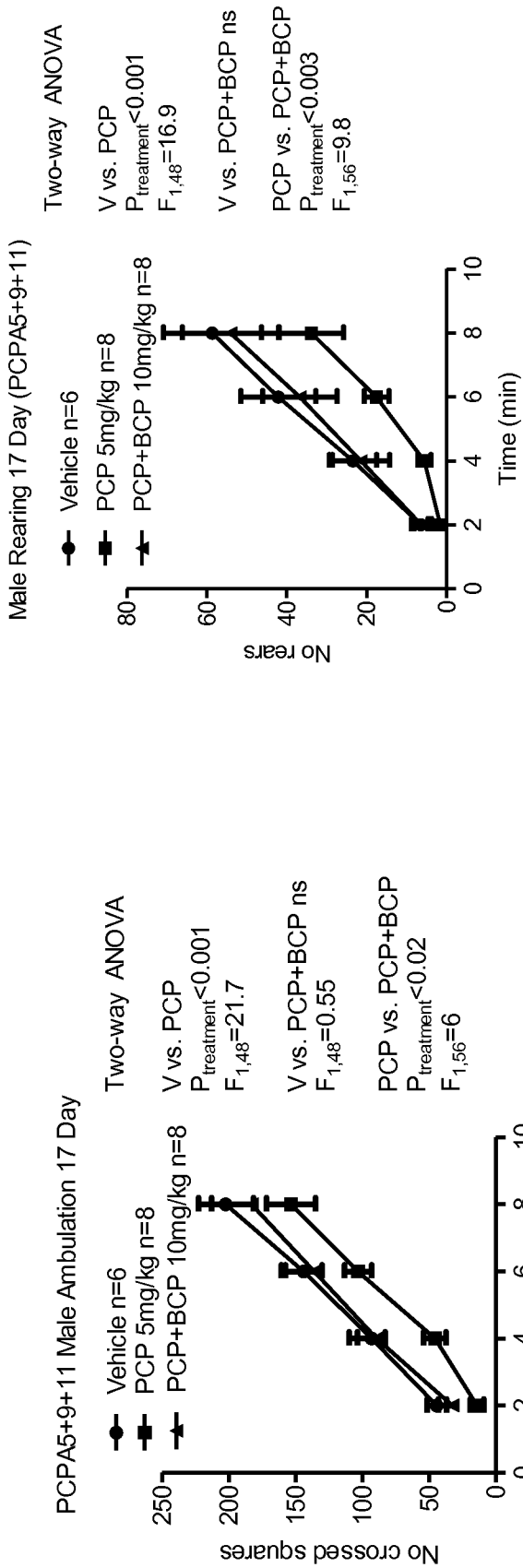


Figure 12A

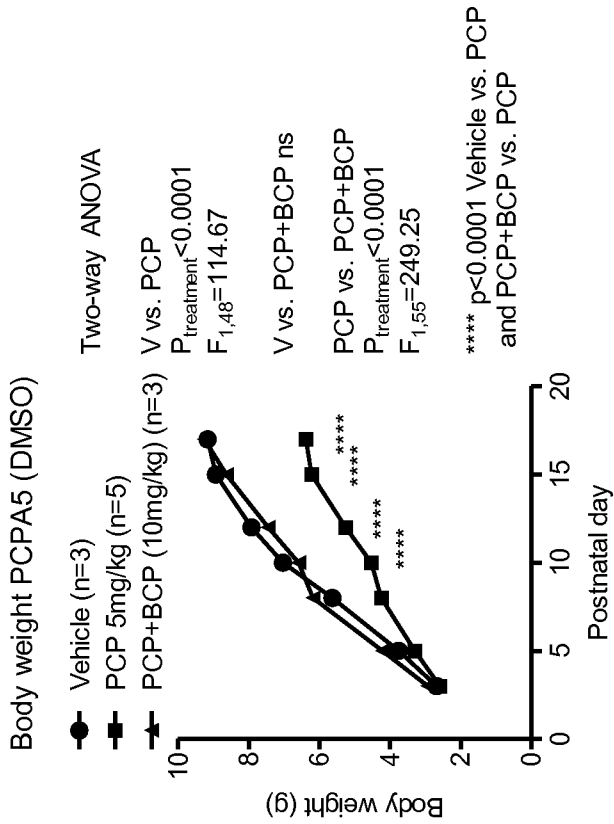


Figure 12B

Figure 12C

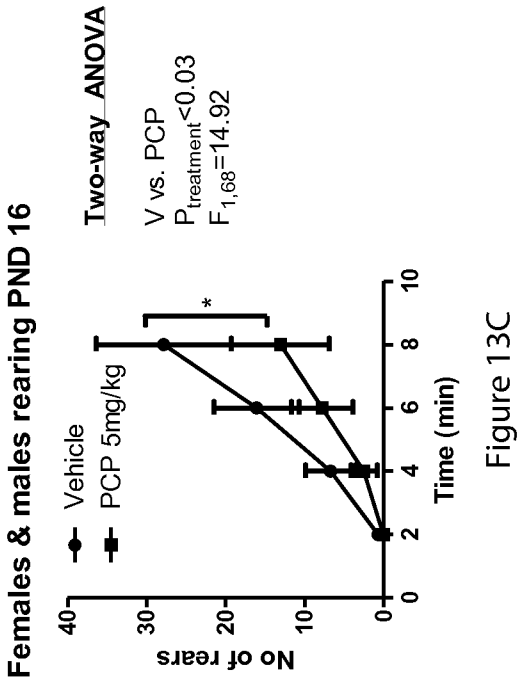
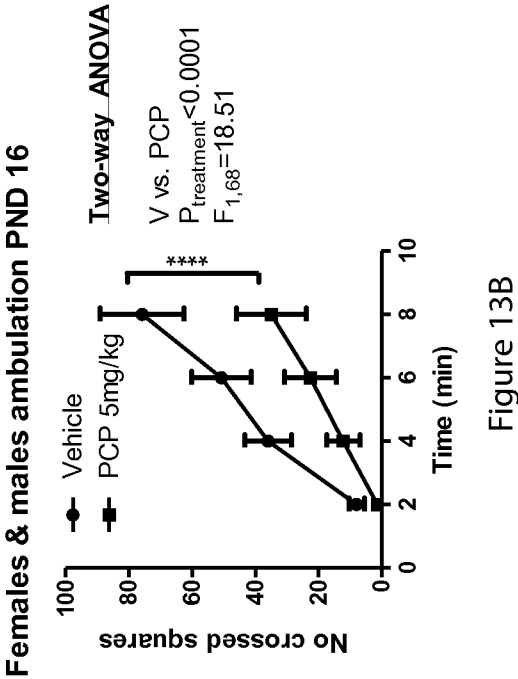
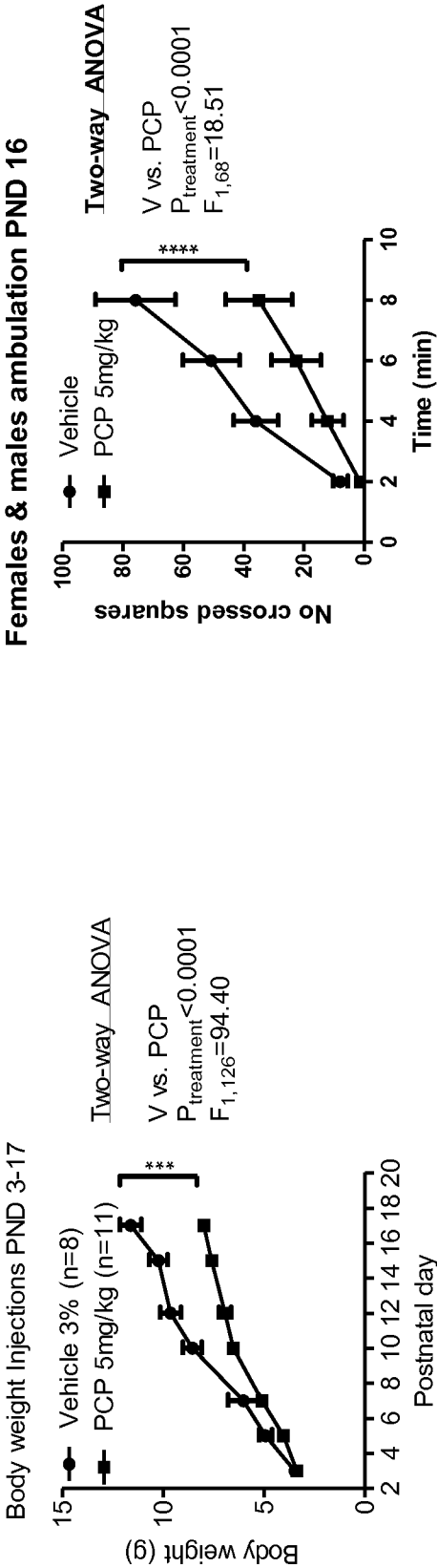


Figure 14A

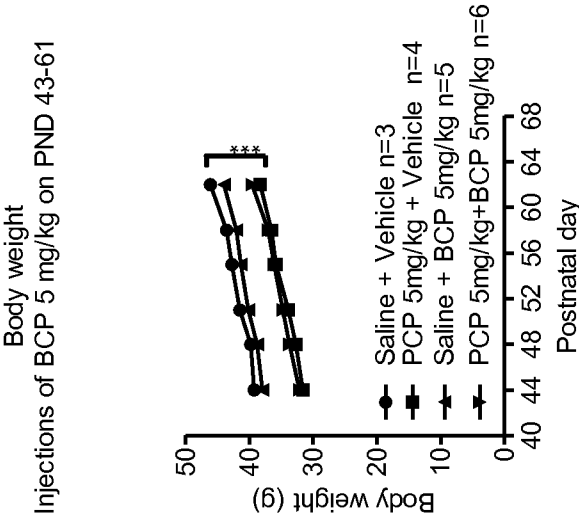
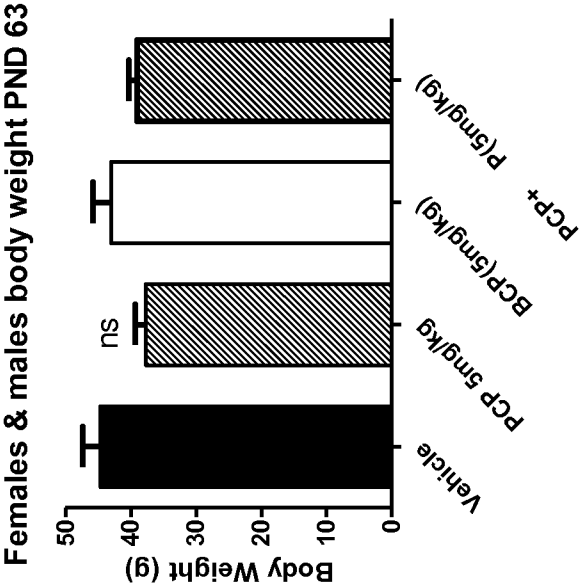


Figure 14B



Two-way ANOVA
V vs. PCP
 $P_{\text{treatment}} < 0.0001$
 $F_{1,30} = 26.31$

PCP vs. BCP
 $P_{\text{treatment}} = 0.0003$
 $F_{1,42} = 15.90$

BCP vs. PCP+BCP
 $P_{\text{treatment}} = 0.0001$
 $F_{1,54} = 17.44$

V vs. PCP+BCP
 $P_{\text{treatment}} < 0.0001$
 $F_{1,42} = 29.13$

PCPA6 Male Ambulation PND 63

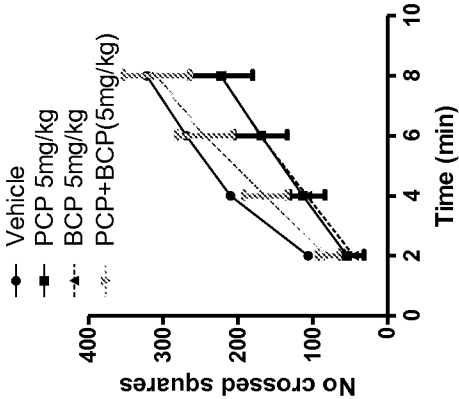


Figure 14C

PCPA6 Female Ambulation PND 63

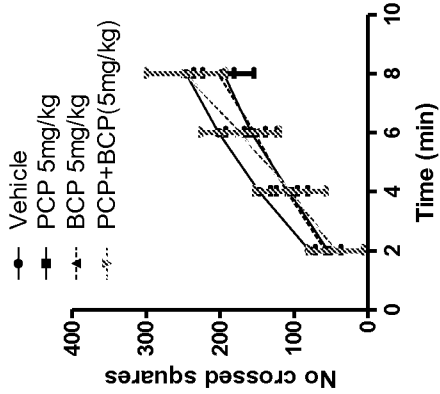


Figure 14D

PCPA6 Females & males ambulation PND 63

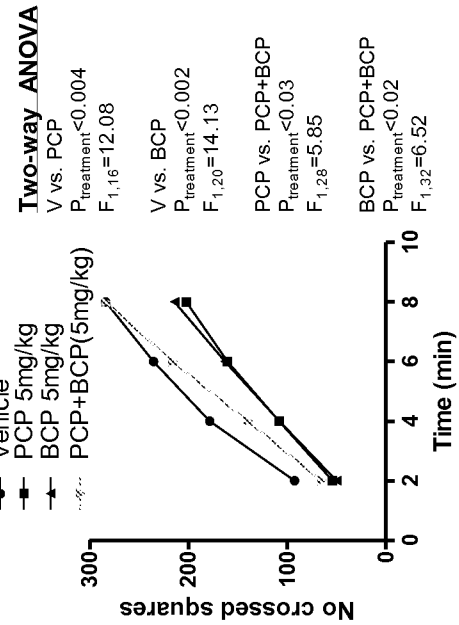


Figure 14E

Females & males rearing PND 63

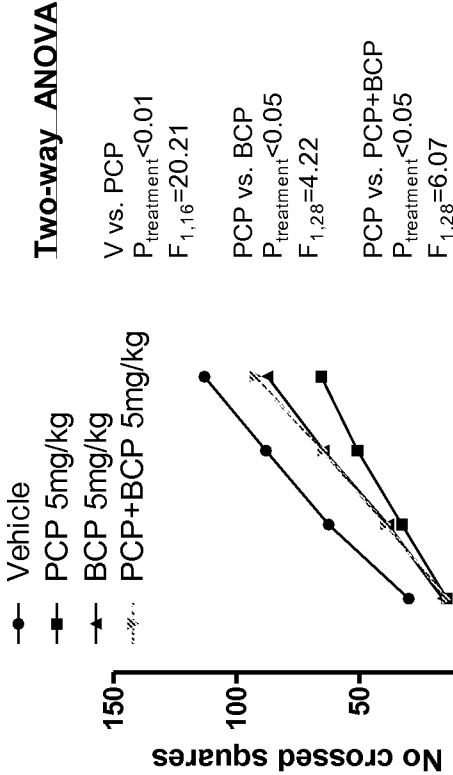


Figure 15A

Male Rearing PND 63

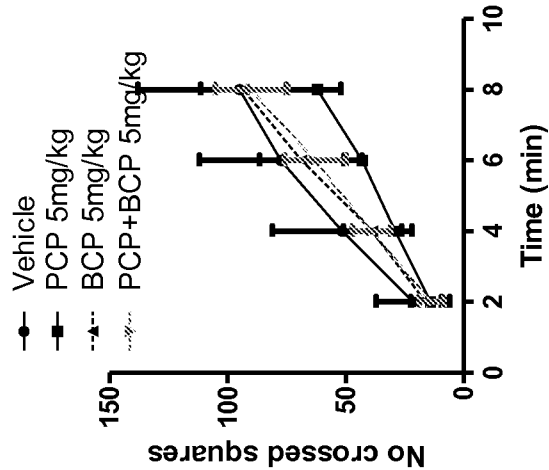


Figure 15B

Female Rearing PND 63

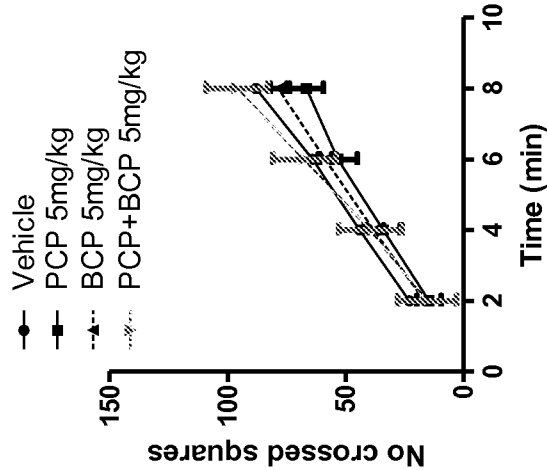


Figure 15C

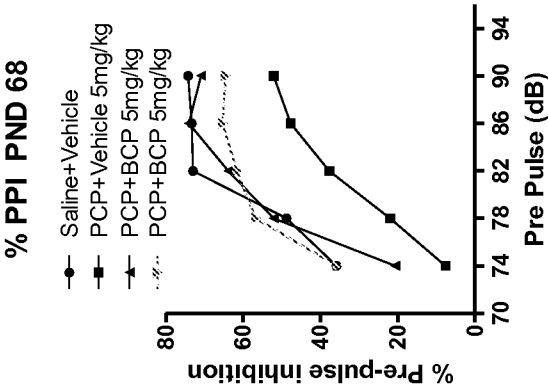


Figure 16A

Two-Way ANOVA
V vs. PCP
 $F_{1,25}=12.46$
 $P_{value}<0.002$
PCP vs. BCP
 $F_{1,35}=13.89$
 $P_{value}=0.0007$
PCP vs. PCP+BCP
 $F_{1,40}=16.38$
 $P_{value}=0.0002$

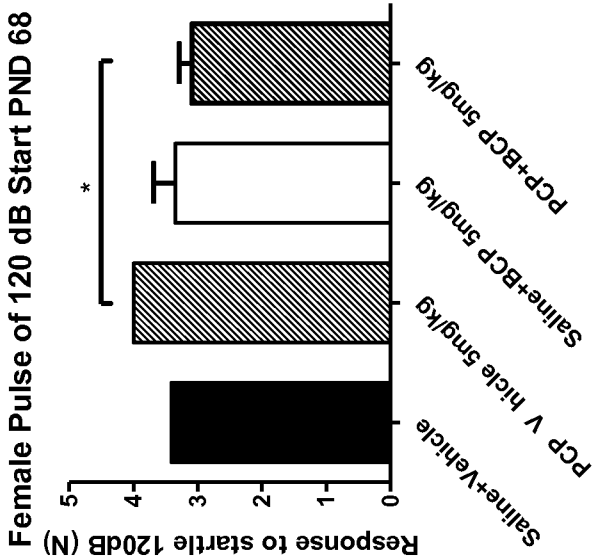


Figure 16B

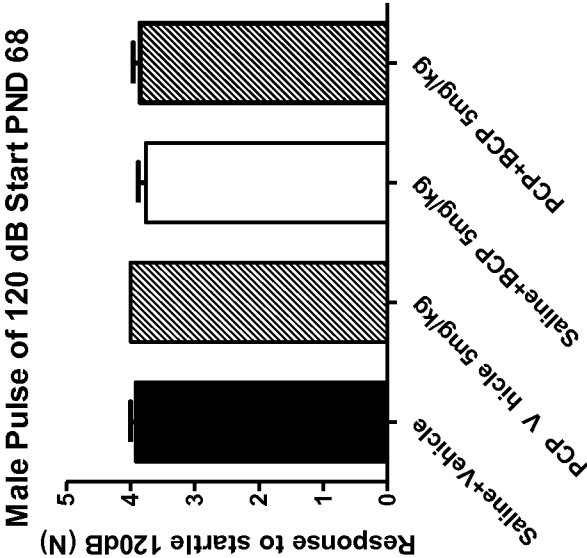


Figure 16C

Female response to tone PND 68

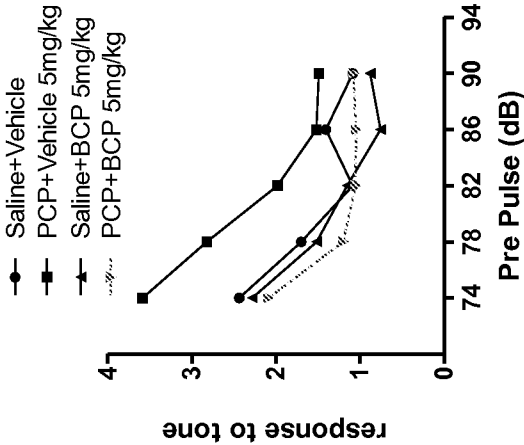


Figure 17B

Male response to tone PND 68

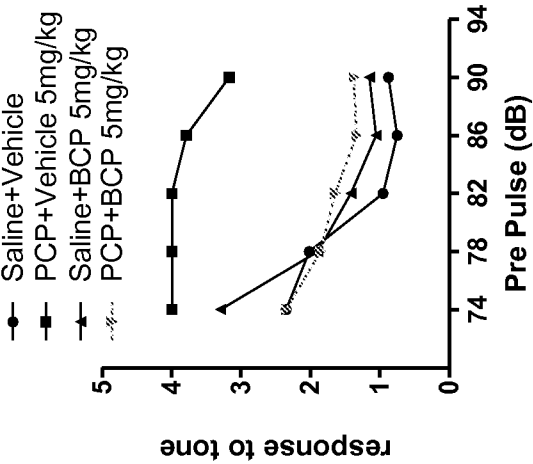


Figure 17C

All response to tone PND 68

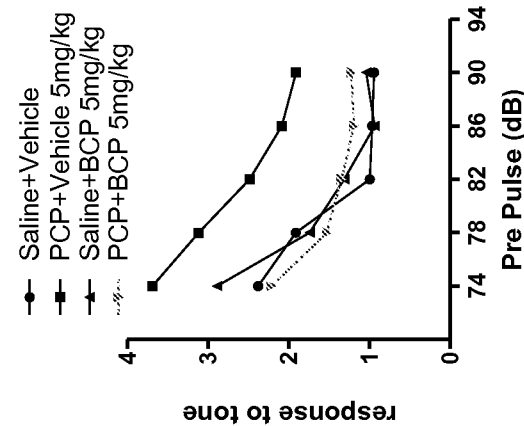


Figure 17A

2- Way ANOVA

V vs. PCP

$F_{1,25}=15.74$

$P_{value}=0.0005$

PCP vs. BCP

$F_{1,35}=18.58$

$P_{value}=0.0001$

PCP vs. PCP+BCP

$F_{1,40}=26.92$

$P_{value}<0.0001$

Pulse of 120DB Finish PND 68

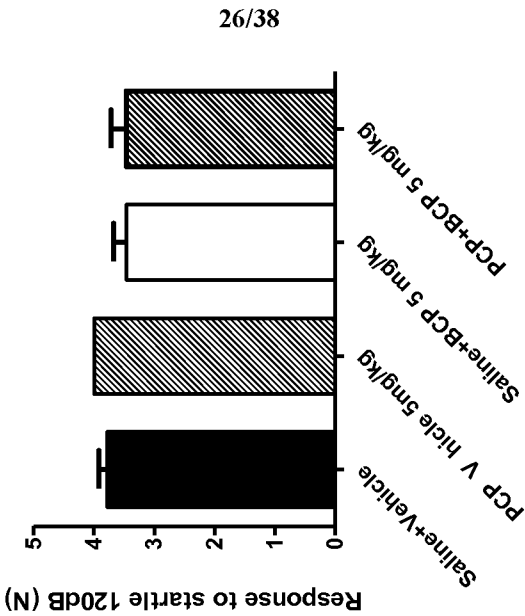


Figure 18C

Male Pulse of 120DB Finish PND 68

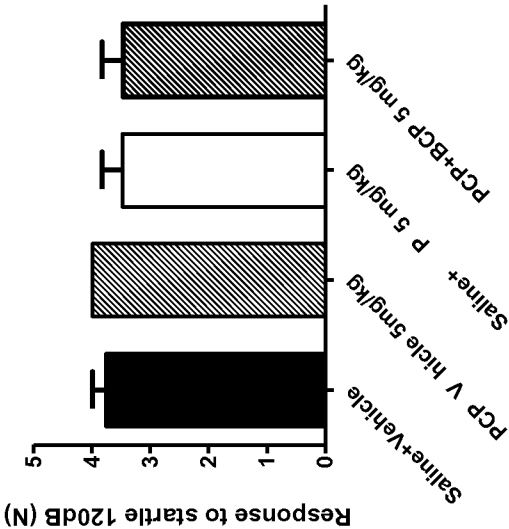


Figure 18B

Female Pulse of 120DB Finish PND 68

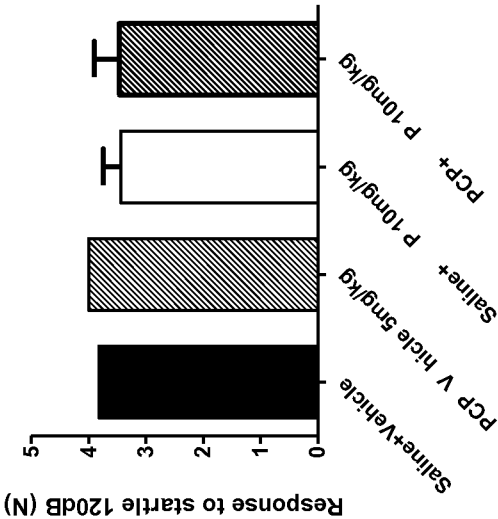


Figure 18A

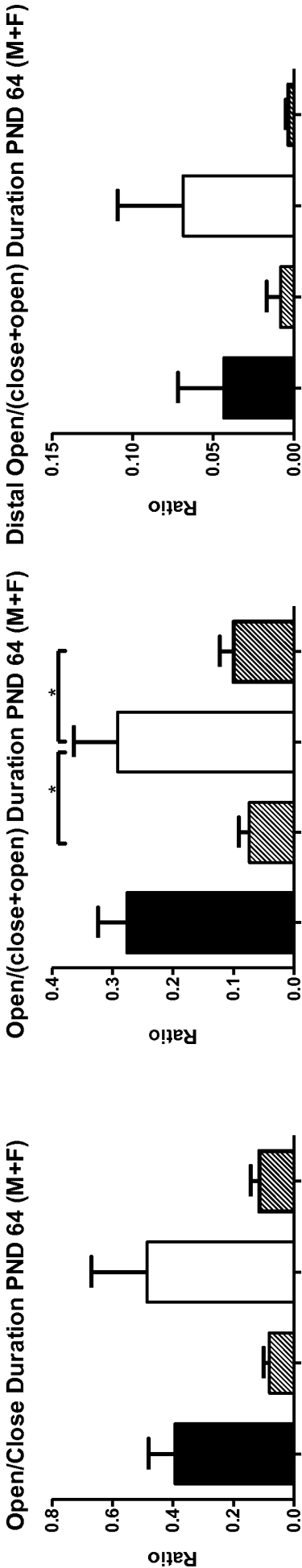


Figure 19A

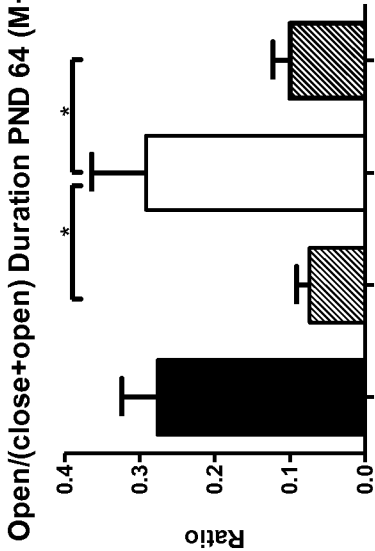


Figure 19B

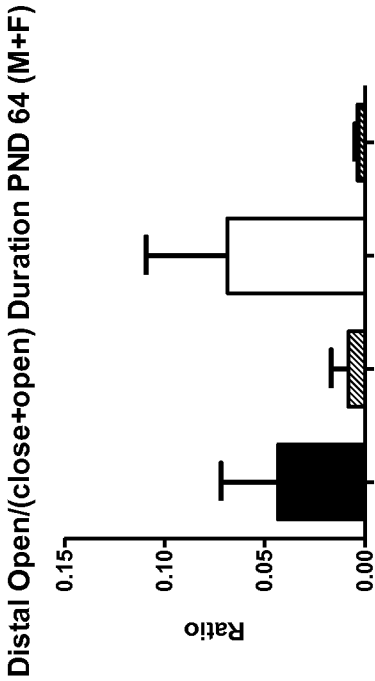


Figure 19C

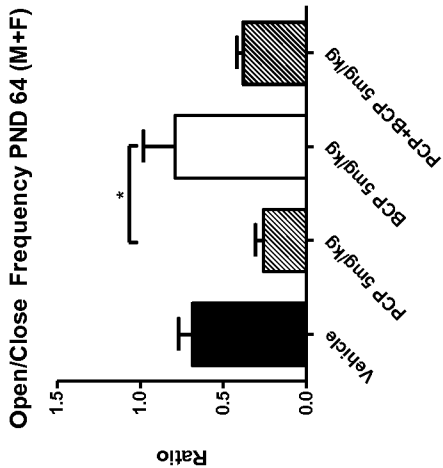


Figure 19D

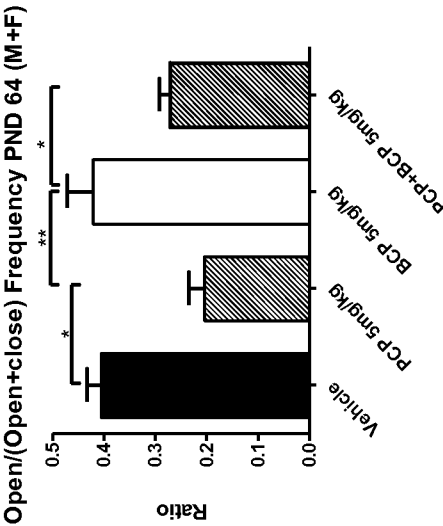


Figure 19E

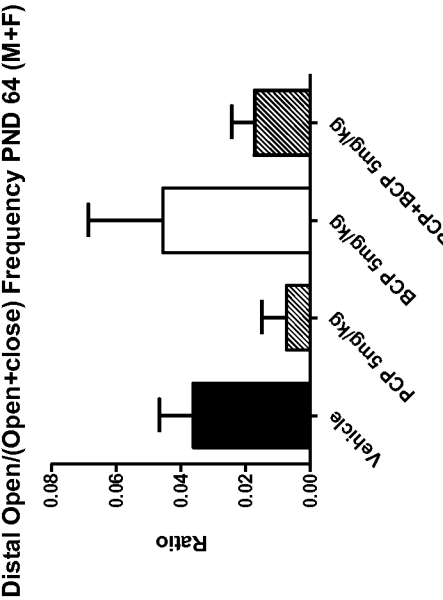


Figure 19F

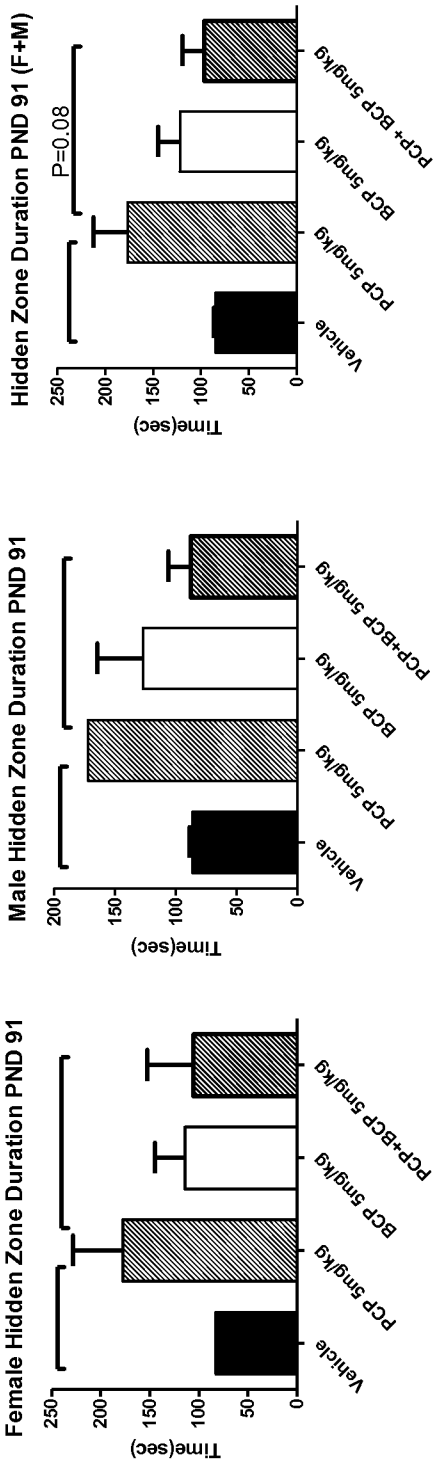


Figure 20C

Figure 20B

Figure 20A

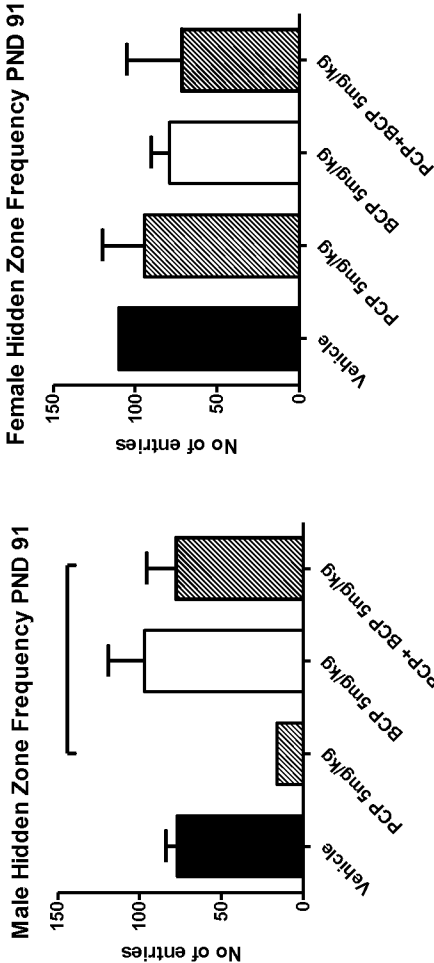


Figure 20E

Figure 20D

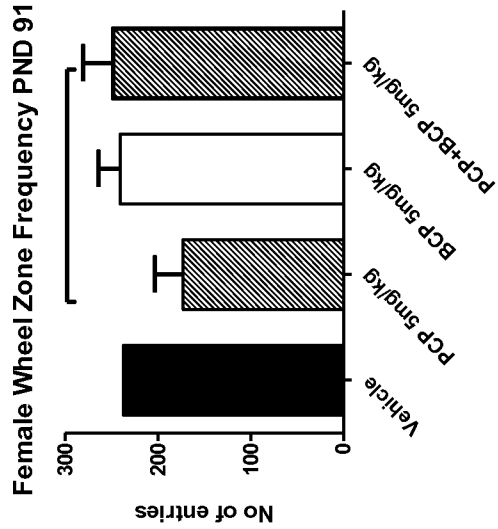


Figure 21A

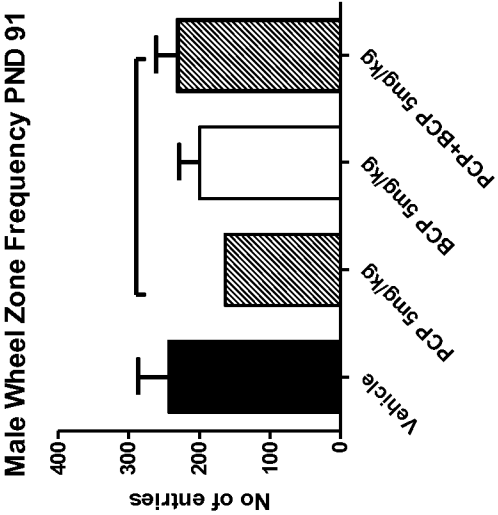


Figure 21B

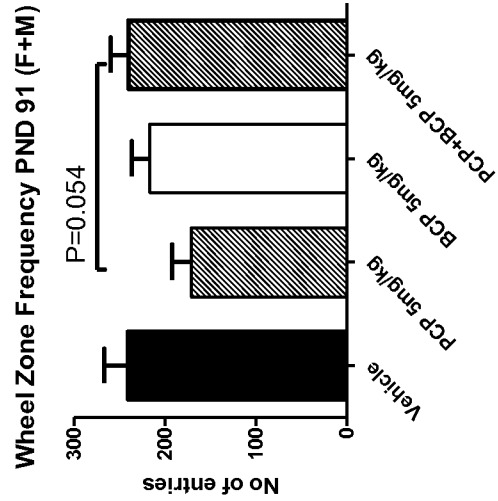


Figure 21C

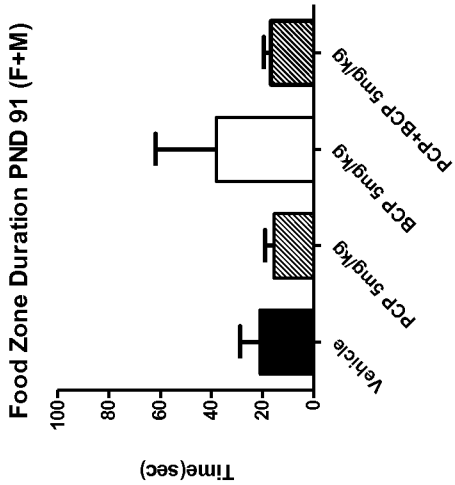


Figure 22C

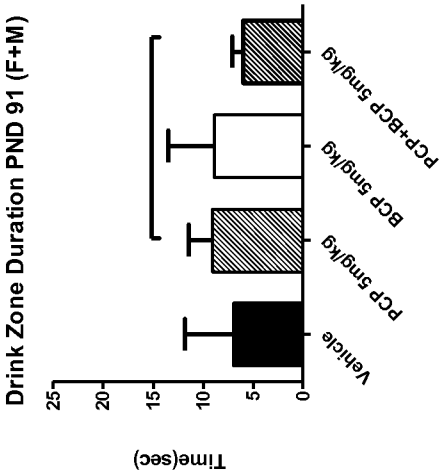


Figure 22F

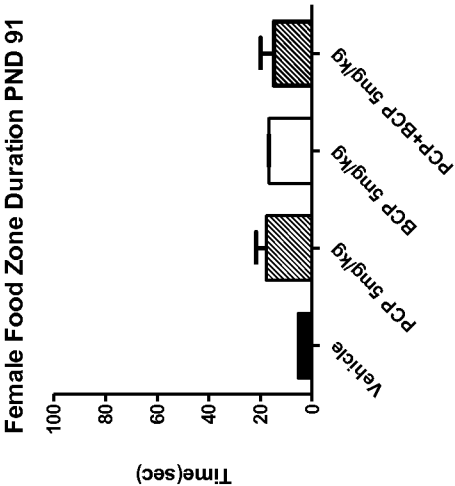


Figure 22B

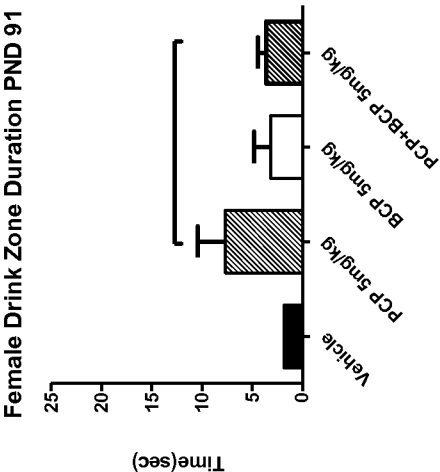


Figure 22E

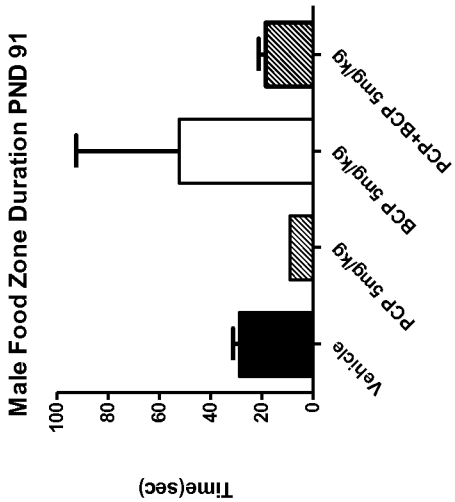


Figure 22A

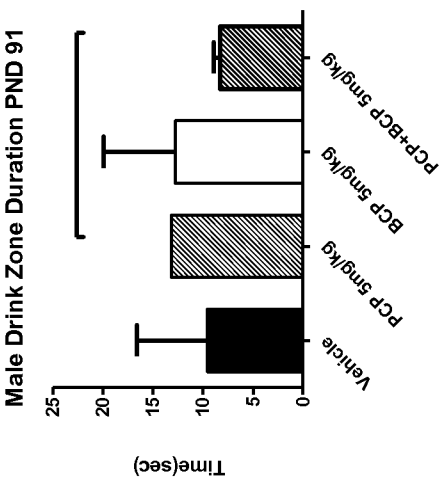


Figure 22D

Female Ambulation PND 104

- Saline+Vehicle
- PCP+Vehicle5mg/kg
- ▲ Saline+BCP 5mg/kg
- ⋯ PCP+BCP(5mg/kg)

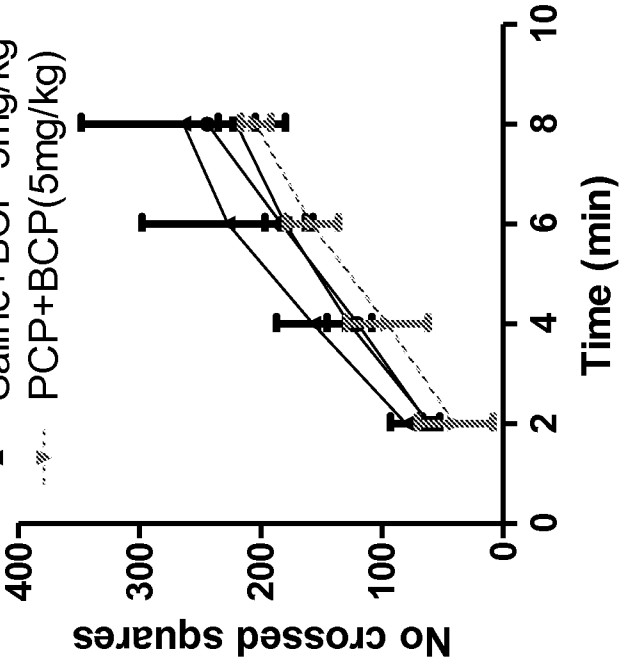


Figure 23A

Male Ambulation PND 104

- Saline+Vehicle
- PCP+Vehicle5mg/kg
- ▲ Saline+BCP 5mg/kg
- ⋯ PCP+BCP(5mg/kg)

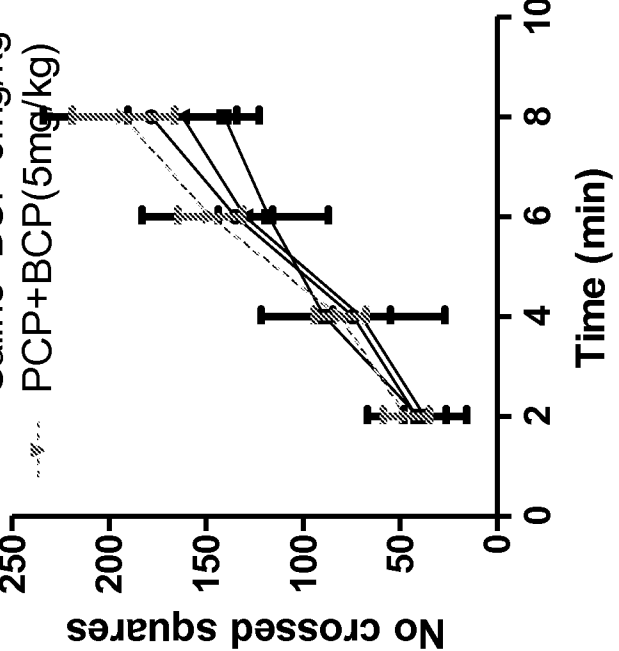
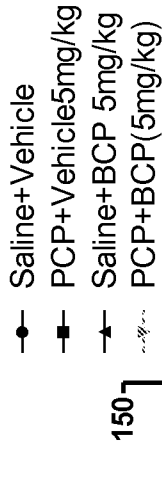
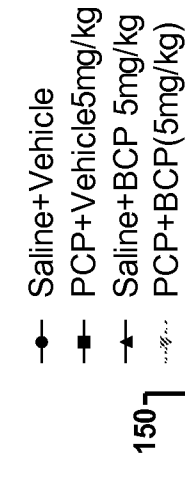


Figure 23B

Female Rearing PND 104



Male Rearing PND 104



Two-way ANOVA

BCP vs. PCP+BCP
 $P_{\text{treatment}} < 0.002$
 $F_{1,16} = 13.80$

Figure 23C

Body weight PND 104 (F+M)

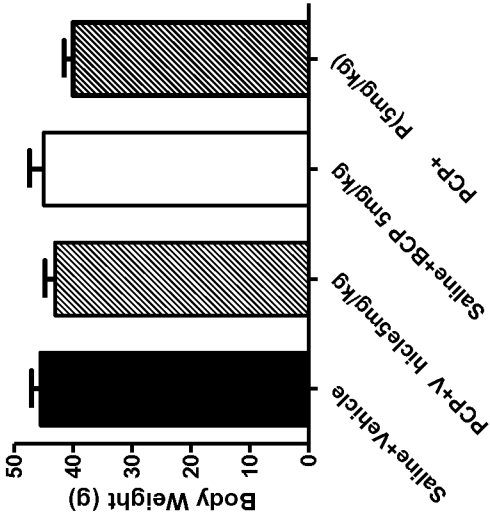


Figure 23E

Figure 23D

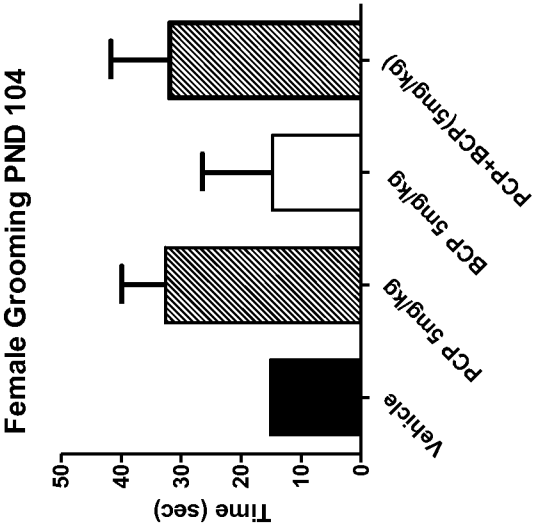


Figure 24A

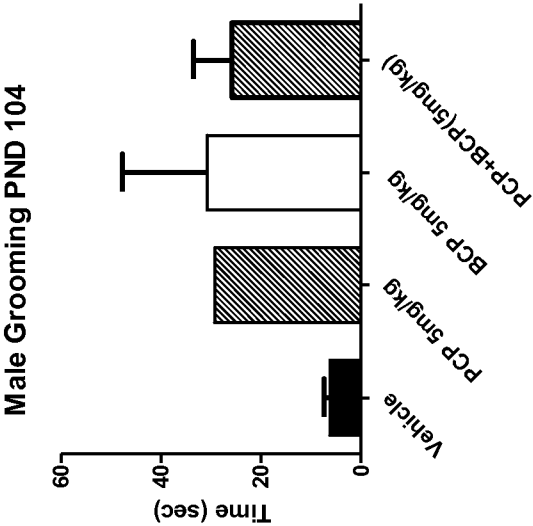


Figure 24B

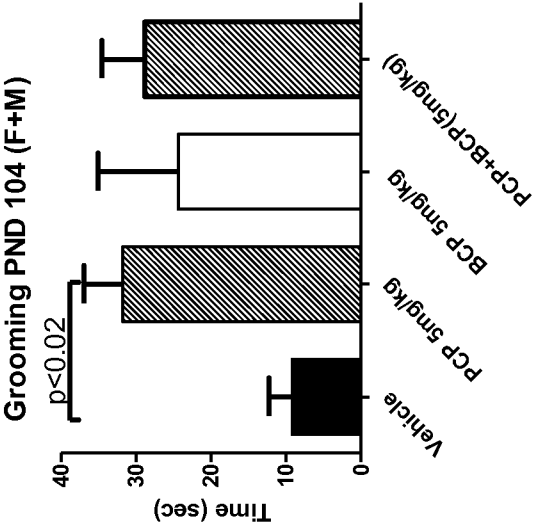


Figure 24C

Figure 25A

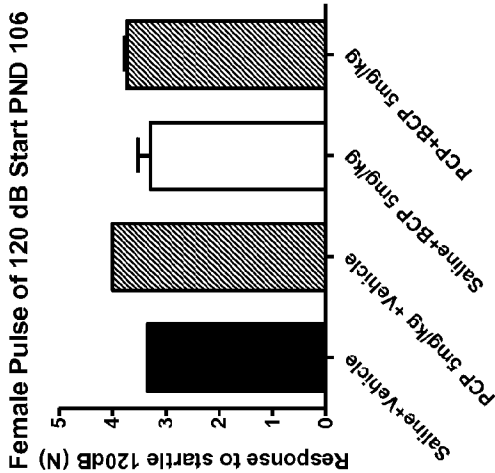


Figure 25B

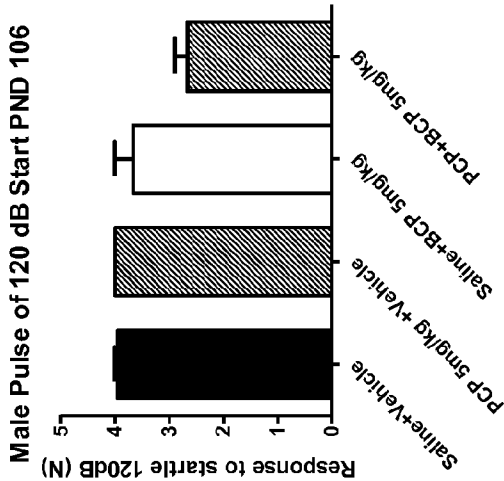


Figure 25C

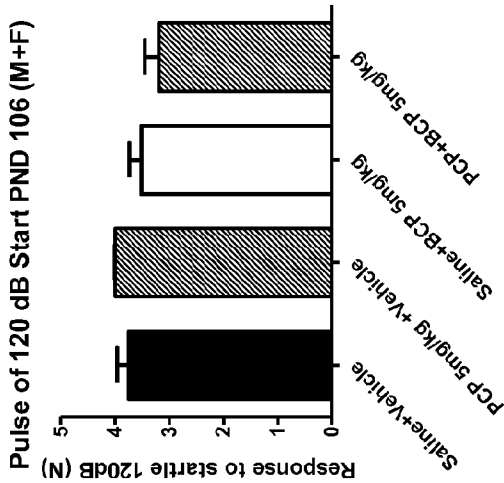


Figure 25D

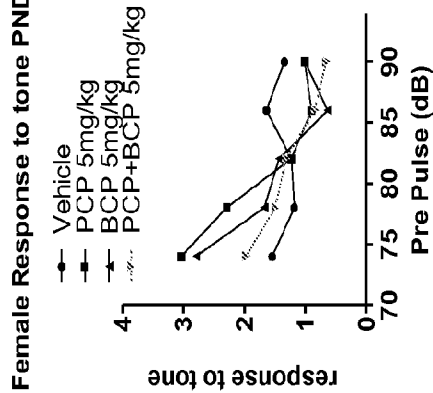


Figure 25E

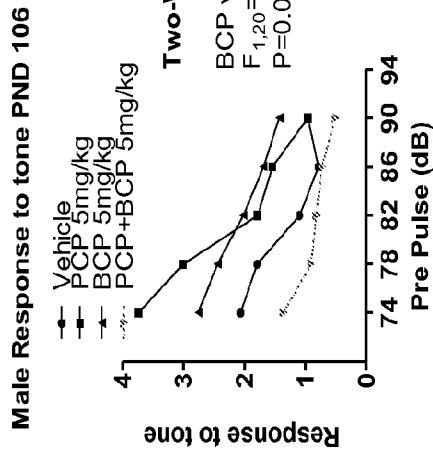
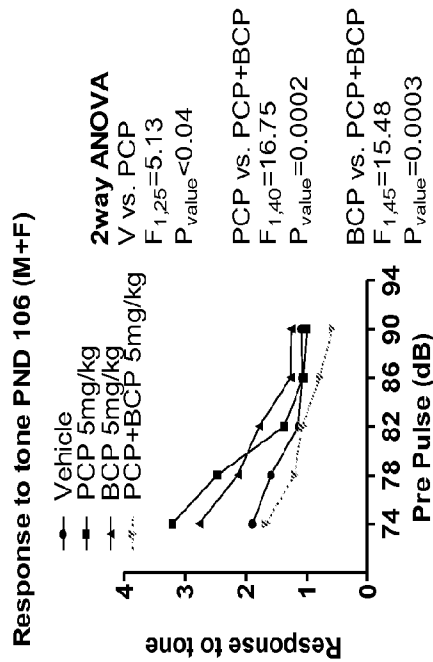


Figure 25F



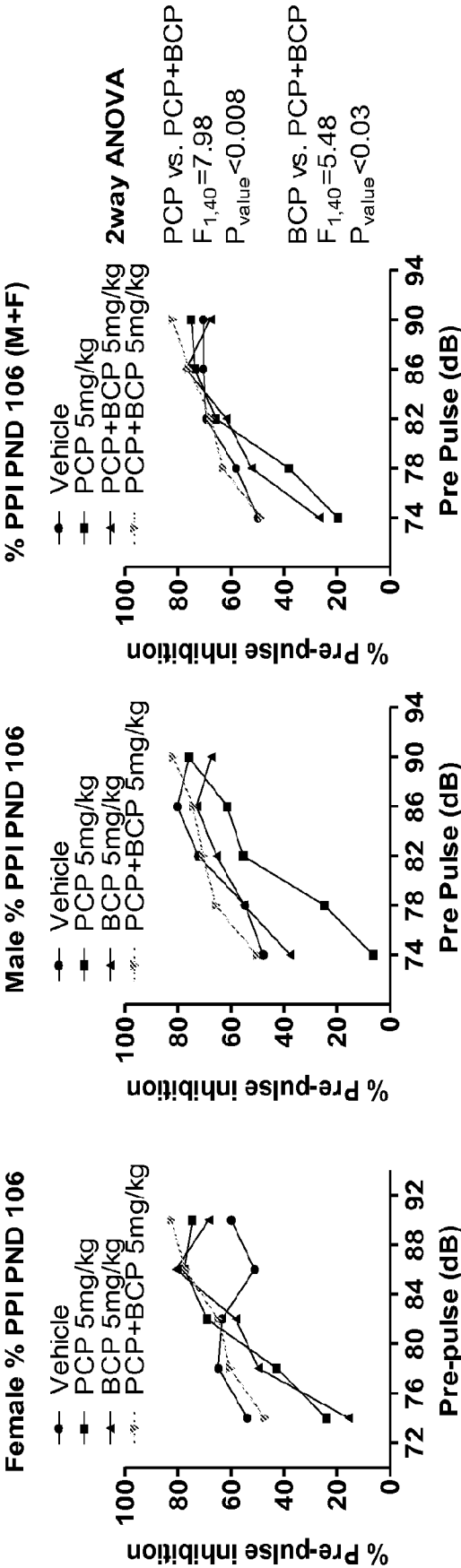


Figure 25I

Figure 25H

Figure 25G

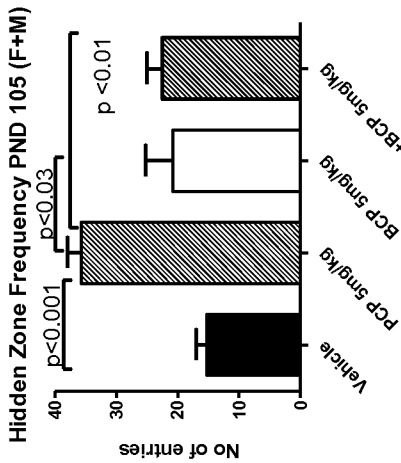


Figure 26C

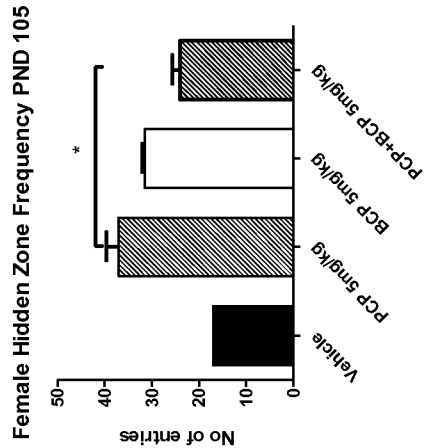


Figure 26B

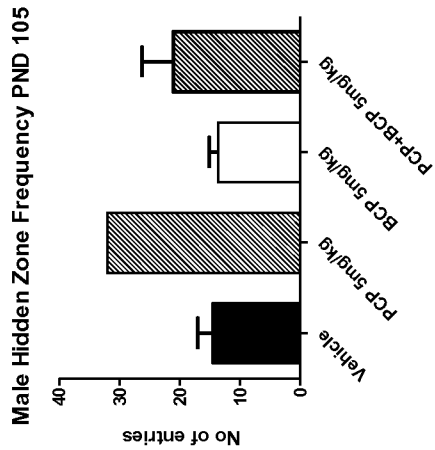


Figure 26A

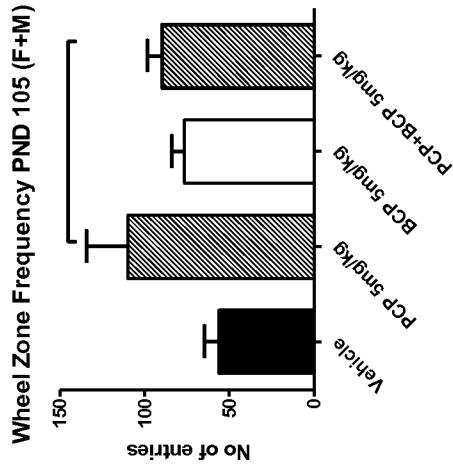


Figure 26F

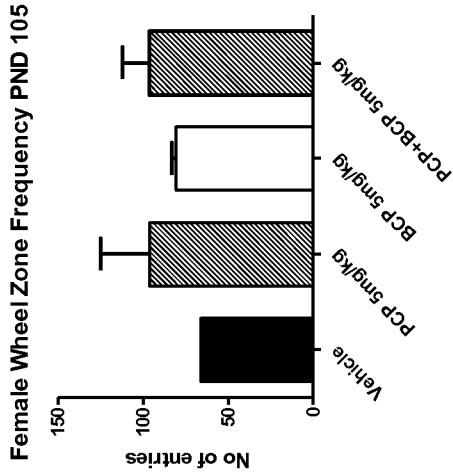


Figure 26E

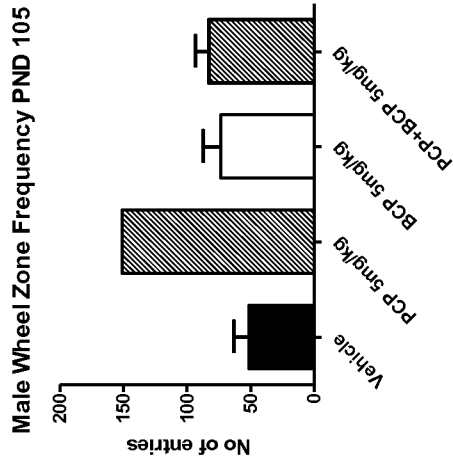


Figure 26D

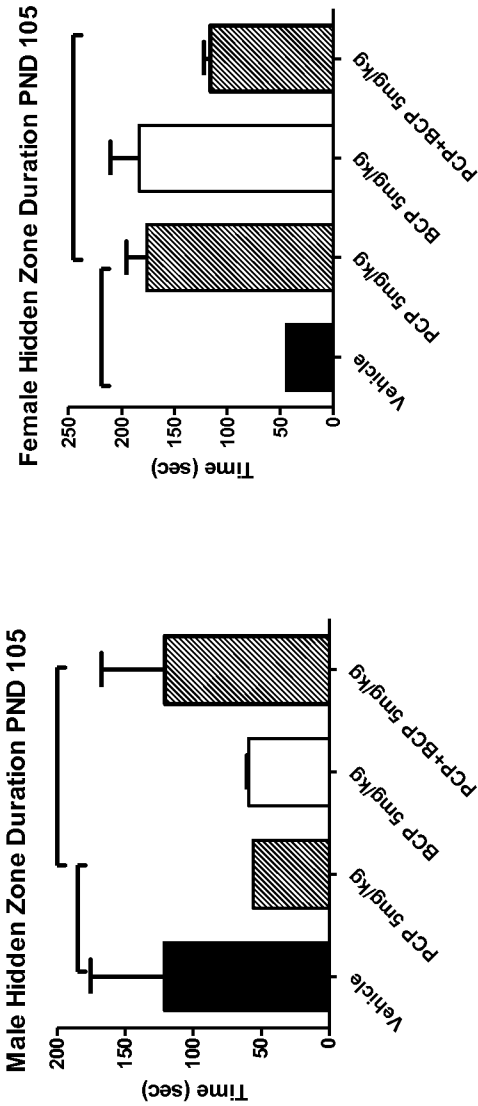


Figure 27A

Figure 27B

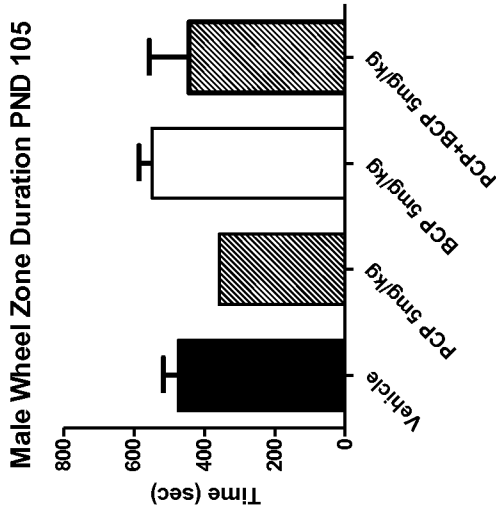


Figure 27C

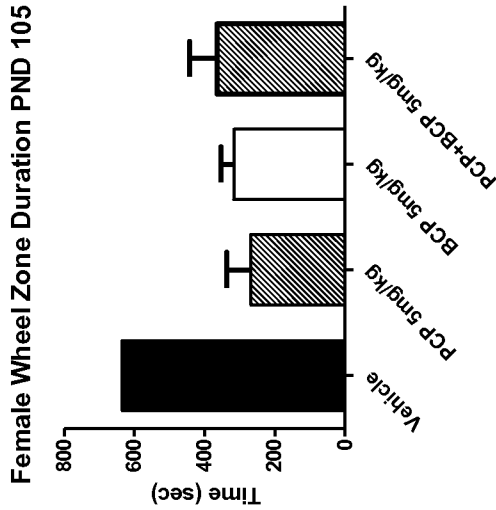


Figure 27D

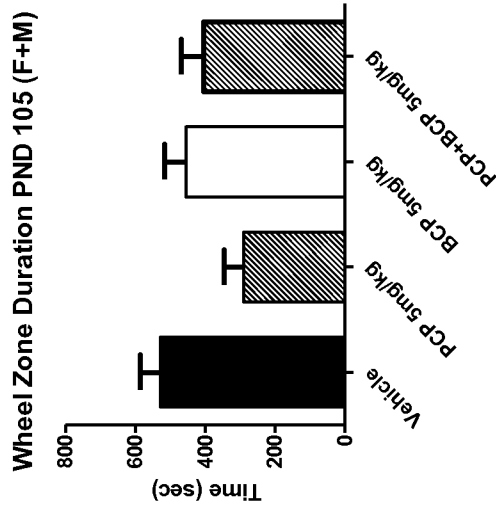


Figure 27E

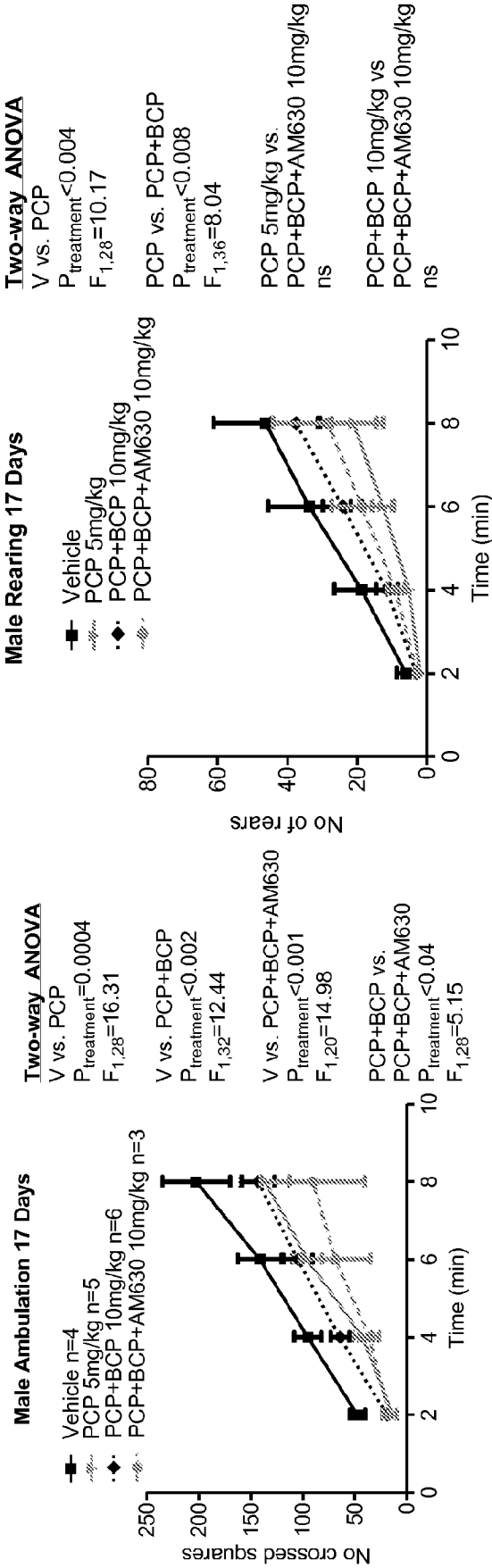


Figure 28A

Figure 28B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2013/052182

A. CLASSIFICATION OF SUBJECT MATTER

IPC (2013.01) A61K 31/015, A61K 36/00, A61P 25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC (2013.01) A61K 31/015, A61K 36/00, A61P 25/18

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See extra sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006017892 A1 ICE NORTHERN SYDNEY AND CENTRA [AU]; COULSTON CARISSA MAREE [AU]; TENNANT CHRISTOPHER CHARLES [AU]; PERDICES MICHAEL [AU] 23 Feb 2006 (2006/02/23) page 7, line 36 - page 8, line 2; page 8, lines 21-29; example 2-3; claims	30-32
Y		1-32
Y	"Brain CB2 Receptors: Implications for Neuropsychiatric Disorders", Michelle Roche and David P Finn, Pharmaceuticals 2010, 3, 2517-2553 10 Aug 2010 (2010/08/10) pages 2532-2534, chapter 5.3. "Schizophrenia"; Page 2535, chapter 6."Conclusions and Future Directions"; Figure 2	1-29
Y	"Beta-caryophyllene is a dietary cannabinoid", Jurg Gertsch et al., Proc Natl Acad Sci, 2008 July 1;10(26): 9099-9104 23 Jun 2008 (2008/06/23) abstract	1-29

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 Jul 2013

Date of mailing of the international search report

18 Jul 2013

Name and mailing address of the ISA:

Israel Patent Office

Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel

Facsimile No. 972-2-5651616

Authorized officer

AMITAY Noam

Telephone No. 972-2-5651725

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2013/052182

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>"Ambulation-promoting effect of peppermint oil and identification of its active constituents", Toyoshi Umezu et al., Pharmacology Biochemistry and Behavior Volume 69, Issues 3-4, 8 July 2001, Pages 383-390</p> <p>01 Jul 2001 (2001/07/01) abstract</p>	1-29

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2013/052182

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet):

* This International Searching Authority found multiple inventions in this international application, as follows:

- | | | |
|---------------|--|---------------|
| Invention/s 1 | A composition comprising beta-caryophyllene (BCP) and a pharmaceutically effective carrier for use in treating schizophrenia, use of BCP and a pharmaceutically effective carrier in the manufacture of a composition for treating schizophrenia in a subject in need thereof and a method for treating schizophrenia in a subject in need thereof comprising administering a therapeutic composition comprising BCP and a pharmaceutically effective carrier. | Claim/s 1-29 |
| Invention/s 2 | A composition comprising a CB2 receptor agonist and a pharmaceutically effective carrier for use in treating schizophrenia, use of a composition comprising a CB2 receptor agonist and a pharmaceutically effective carrier in the manufacture of a composition for treating schizophrenia in a subject in need thereof, and a method for treating schizophrenia in a subject in need thereof, the method comprising administering a therapeutic composition comprising a CB2 receptor agonist and a pharmaceutically effective carrier. | Claim/s 30-32 |

B. FIELDS SEARCHED:

* Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases consulted: SCIRUS, THOMSON INNOVATION, Esp@cenet, Google Patents, CAPLUS, WPI Data, EPODOC, Google Scholar

Search terms used: beta-caryophyllene, Caryophyllene, ?-caryophyllene, BCP, Sesquiterpene, (Clove or hemp or cannabis* or rosemar*) near oil, schizophren*, mental near disorder, antipsycho* agent*, CB2 receptor, Cannabinoid receptor

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IB2013/052182

Patent document cited search report			Publication date	Patent family member(s)			Publication Date
WO	2006017892	A1	23 Feb 2006	WO	2006017892	A1	23 Feb 2006
