Cholecystokinin receptor subtypes: role in the modulation of anxiety-related and reward-related behaviours in animal models

Susan Rotzinger, PhD; Franco J. Vaccarino, PhD

Centre for Addiction and Mental Health, and Departments of Psychiatry and Psychology, University of Toronto, Toronto, Ont.

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Cholecystokinin (CCK) is an abundant and widely distributed neuropeptide that plays a modulatory role in a variety of behaviours. This paper focuses on the role of CCK in modulating anxiety-related and reward-related behaviours in key brain regions of the amygdala and mesolimbic dopamine system, respectively. The role of CCK in mediating aspects of these behaviours has been studied in a variety of behavioural paradigms, but inconsistent results have led to confusion regarding the precise role of the receptor subtypes in mediating behaviour. The confusion in the literature may come in part from the diverse behavioural paradigms that are used, the differences in regional effects of CCK manipulations in different areas and at different receptor subtypes in these areas and the dependence of the behavioural outcome on the baseline state of arousal of the animal. Evidence on the role of CCK in anxiety-related and reward-related behaviours in various animal models indicates that CCK-B receptors in the basolateral amygdala are important mediators of anxiety-related behaviours and that CCK-A and CCK-B receptors in the nucleus accumbens are important in mediating different aspects of reward-related behaviour. Emphasis is placed upon the role of CCK as a neuromodulator that is recruited only under conditions of high frequency neuronal firing.

La cholécystokinine (CCK) est un neuropeptide abondant et largement distribué qui joue un rôle de modulateur dans toutes sortes de comportements. Ce document porte avant tout sur le rôle de la CCK dans la modulation des comportements reliés à l’anxiété et à la récompense dans des régions clés du cerveau que sont le noyau amygdalien et le système de la dopamine mésolimbique, respectivement. On a étudié le rôle de la CCK dans la médiation d’aspects de ces comportements dans un éventail de paradigmes comportementaux, mais des résultats erratiques ont suscité la confusion au sujet du rôle précis des sous-types de récepteurs dans la médiation du comportement. La confusion qui règne dans les publications peut découler en partie des divers paradigmes comportementaux utilisés, des différences au niveau des effets régionaux de manipulations de la CCK dans des régions différentes et des sous-types de récepteurs différents dans ces régions, et de la dépendance du résultat comportemental à l’égard de l’état d’éveil de
Introduction

Cholecystokinin (CCK) has been strongly linked to anxiety and panic,1–3 and evidence suggests an involvement with numerous other mental illnesses such as schizophrenia4–9 and addictions.10–15 Although CCK has been studied in great detail in a wide variety of paradigms, there is still a lack of consensus regarding the roles of CCK-A and CCK-B receptor subtypes in mediating different aspects of behaviour.

This paper provides a brief review of the preclinical behavioural data investigating the role of CCK in anxiety and reward-related behaviours and provides a hypothesis for the differential roles of CCK-A and CCK-B receptors in mediating these behaviours. In particular, evidence is presented for the role of CCK-B receptors in mediating the acute effects of stress and psychostimulants and for CCK-A receptors in mediating more long-term effects of stress and psychostimulants. Emphasis is placed on the importance of the testing conditions used, because often the effects of CCK receptor manipulations are seen only when an organism is in a potentiated behavioural state, and not under baseline conditions. The findings emphasize the role of CCK as a neuromodulator under “potentiated” behavioural conditions. This modulatory function arises from the evidence that peptides and classical transmitters, though colocalized, are differentially stored and released in the nerve terminal, thus allowing for greater flexibility in message transmission.

Neurobiology of CCK

CCK was originally identified in the gut, where it is involved in the secretion of pancreatic enzymes, gallbladder contractions and gut motility. However, it is more abundant in the brain than in the periphery and is one of the most abundant neuropeptides in the brain.16,17 Its concentration in cortex and limbic regions18,19 supports its role in the regulation of many behavioural phenomena, including satiety and appetite,20 thermoregulation,21,22 sexual behaviour,23,24 anxiety,20,25 memory26 and response to drugs of abuse.27

The neurobiology of CCK has been extensively reviewed elsewhere,16,28 and therefore only a brief summary is presented here. CCK meets the criteria for designation as a neurotransmitter;16 it has neurotransmitter-like properties in that it is synthesized de novo,29 is released via a calcium-dependent mechanism30 and is active at both CCK-A and CCK-B receptor subtypes.31 Pre-pro CCK is a 115-amino-acid peptide that is cleaved into smaller biologically active fragments.32 CCK-8, sulphated at the tyrosine residue, is the most abundant form of CCK in the brain.19,28 CCK is also cleaved into other biologically active fragments, such as CCK-4 and CCK-5.

CCK peptides bind to 2 receptors, CCK-A (also called CCK-1) and CCK-B (also called CCK-2).32,33 CCK-A receptors are more abundant in the periphery than in the brain, but in the rat brain they have been localized in the nucleus accumbens (NAcc), area postrema, interpeduncular nucleus, nucleus tractus solitarii, medialis preoptic area, arcuate nucleus, circumventricular regions of hypothalamus, septum, stria terminalis, habenula, substantia nigra, ventral tegmental area (VTA) and lateral geniculate nucleus, as well as the medulla and dorsal horn of the spinal cord.34–38 CCK-B receptors are more abundant in the brain than in the periphery and are found throughout the cortex and in the basal ganglia, striatum, presubiculum, amygdala, mamillary bodies, cerebellar cortex, pineal gland, striatum and nucleus accumbens.38,39 Both receptor types have been suggested to exist in more than 1 affinity state,40,41 which adds to the complexity of this system, although little is known about these different affinity states at this time. CCK-A receptors are highly selective for the sulphated octapeptide, CCK-8S,28,35 whereas CCK-B receptors show equal affinity for CCK-8S, CCK-8U, CCK-5 and CCK-4.21,42,43

CCK is colocalized in cell bodies and terminals with many other neurotransmitters such as gamma-aminobutyric acid (GABA),44,45 dopamine (DA),46 serotonin47 (5-HT) and opiates.48 For the purposes of this paper, it
is especially interesting to note that CCK is colocalized with DA in 80%–90% of VTA DA cell bodies and that terminals containing both CCK and DA are present in the caudal-medial NAcc, bed nucleus of the stria terminalis and central nucleus of the amygdala, among other areas. There is also evidence of a major corticostriatal CCK-containing pathway that is thought to contain glutamate as well.

Neuropeptides are often colocalized with classical neurotransmitters, where they play either a neurotransmitter or neuromodulatory role. In many areas where CCK is colocalized with DA, the concentration of CCK is more than an order of magnitude greater than the concentration of DA. Colocalization of transmitters and peptides allows for a greater diversity of message transmission. The differential storage of peptides and transmitters in large dense-core vesicles and small clear synaptic vesicles, respectively, allows for differential release, which is dependent on the frequency of action potentials. Short, low frequency stimulation results in an increase in Ca²⁺ concentration only in the local area directly near the Ca²⁺ channels, and this increase in Ca²⁺ is quickly sequestered and suppressed by various uptake and buffering systems within the terminal. Thus, only the small clear vesicles, which reside near the active zone, are released. The large dense-cored vesicles that store peptide are randomly distributed in the terminal, and only under conditions of synchronous, high frequency firing do the Ca²⁺ concentrations rise to sufficient levels to cause release of neuropeptide from these vesicles. Therefore, higher frequencies or bursts of impulses are required to increase the Ca²⁺ concentrations enough to result in release of peptide.

This is likely the mechanism by which CCK is coreleased with DA at high frequency firing rates, allowing the possibility of modulating DA function, but only under conditions that lead to this high frequency firing. This is a very important concept with regard to the behavioural effects of CCK agonist and antagonist manipulations and will be explored further in the sections that follow. This colocalization and differential release of CCK with other neurotransmitters is likely a key mechanism through which CCK has modulatory influences on anxiety and reward-related behaviours.

Role of CCK in anxiety

The role of CCK in anxiety is quite well established in the literature; the acute anxiogenic effects of CCK appear to be the result of activation of CCK-B receptors in the basolateral amygdala. Intravenous infusions of CCK-4 can induce panic attacks in patients with panic disorder and in healthy individuals. Evidence implicating CCK-B receptors in panic includes the much higher affinity of CCK-B than CCK-A receptors for CCK-4 and the finding that the CCK-B antagonist L-365,260 blocks CCK-4-induced panic attacks. The CCK fragment pentagastrin also increases anxiety in the human social interaction test and anxious-type vervet monkeys display frozen immobility, self-clasping, covering and huddling in response to a challenge dose of CCK-4. The anxiety-provoking effects of CCK agonists have been well documented in rodent models and using a variety of behavioural measures, which are summarized below.

Elevated plus maze

The elevated plus maze (EPM) is a validated model of anxiety that consists of a plus-shaped maze with 2 open arms and 2 enclosed arms. The number of entries to and time spent on the open arms of the maze is a measure of anxiety, with greater open-arm time and entries associated with decreased anxiety. Although this test has been validated for a number of anxiolytic and anxiogenic drugs, it is important to consider the species, methodologic factors, specific receptor ligand and doses used in studies with CCK — results vary greatly depending upon these factors. It has also been suggested that the EPM may not be an appropriate test for assessing the behavioural effects of CCK agonists. Nevertheless, CCK-8 and caerulein, non-selective CCK agonists, injected systemically or into the amygdala, are reported to be anxiogenic in both rats and mice in the EPM, although there is one report of no effect of CCK-8 or CCK-4 on anxiety in the EPM. CCK-B agonists such as the butyrylcarbonyl tetrapeptide of CCK (BOC-CCK-4) and pentagastrin increase anxiety in the EPM, and BOC-CCK-4 also reverses morphine-induced anxiolytic effects in the EPM. The CCK-B antagonists CI-988 and L-365,260 also produce anxiolytic-like effects in this test in rats and mice. However, in another study, the CCK-B antagonists CI-988 and CAM1028 did not affect behaviour in controls but did attenuate increases in anxiety associated with ethanol withdrawal in both rats and mice. These apparently conflicting results may in part be related to the role that CCK plays mainly as a neuro-
modulator — that is, CCK antagonists on their own may not affect baseline anxiety behaviour, but they may instead “modulate” heightened states of anxiety.

CCK-A receptors have not been studied as often as CCK-B, but MK329, a CCK-A antagonist, was found to be a less potent anxiolytic than CCK-B antagonists.\(^7\) Also, in contrast to the anxiolytic effects of CCK-B antagonists, the CCK-A antagonist CAM1481 had little effect on ethanol-withdrawal-induced anxiety in the EPM.\(^8\) Rats lacking CCK-A receptors show increased anxiety in the EPM, but these results are difficult to interpret because these animals have been without CCK-A receptors throughout development\(^9\) and consequent compensatory changes are unclear.

**Acoustic startle tests**

The 2 forms of the acoustic startle paradigm that have been widely used to test anxiety in primates and rodents are the simple acoustic startle response and the fear-potentiated startle. Both measure an animal’s natural response to a fear-provoking stimulus (i.e., sudden loud noise). The fear-potentiated startle uses classical conditioning to condition a fear response to the presentation of a light by pairing the light with footshock. Subsequently, if the light is presented (without footshock) before the presentation of an acoustic startle stimulus, the startle response is potentiated.

Intracerebroventricular (ICV) or intra-amygdala infusions of the CCK-B agonist pentagastrin dose-dependently potentiate acoustic startle responses, at some doses by as much as 90% over baseline responses.\(^10\) A series of discrete, localized injections into a variety of structures showed that the basolateral nucleus of the amygdala is an important site for the anxiogenic effects of CCK-B agonists; infusions of pentagastrin into the basolateral nucleus increased acoustic startle, but infusions into other structures, such as the NAcc, did not.\(^11\) Intra-amygdala PD-135,158 (CCK-B antagonist) blocks the potentiation of startle produced by ICV pentagastrin, further suggesting that pentagastrin potentiates startle through CCK-B receptors in the amygdala. However, the CCK-B antagonist L-365,260 did not affect baseline acoustic startle but dose-dependently decreased fear-potentiated startle.\(^12\) This finding again illustrates the neuromodulatory role of CCK and that the anxiolytic effect of CCK-B antagonists is often apparent only in tests measuring a potentiation of anxiety but not under baseline conditions.

**Locomotor activity**

In a novel open field, low activity scores and less time spent in the centre of the open field are associated with increased fearfulness.\(^13\) In a familiar environment, mild stressors increase locomotor behaviour.\(^14\)

Systemic administration of CCK-4 decreases exploration in the open field, and this effect is blocked by CCK-B, but not CCK-A, antagonists.\(^15\) Bilateral injection of CCK-8 into the NAcc decreases horizontal locomotor behaviour, and injections into the amygdala increase locomotion at the lowest dose and decrease it at highest dose.\(^16\)

On their own, the CCK-A antagonists devazepide and PD-140,158 do not affect locomotor behaviour\(^17\) or amphetamine-induced hyperlocomotion. Interestingly though, CCK-A antagonists do attenuate the amphetamine-induced increases in locomotion in rats previously sensitized to psychostimulants,\(^18\) as will be discussed further in the section on sensitization. These findings again emphasize the neuromodulatory role of CCK and the fact that the effects of CCK manipulations may be subtle and detected only when the system is challenged.

**Summary**

Studies published to date support a role of CCK-B receptors in the acute modulation of anxiety\(^19\) and suggest that an important locus of this effect is the basolateral amygdala. CCK-B agonists are anxiogenic, and CCK-B antagonists reduce potentiated states of anxiety but do not appear to affect baseline anxiety responses. CCK-A receptors do not appear to play a significant role in the acute modulation of anxiety. This is consistent with the distribution of CCK-B receptors in areas associated with anxiety, such as the basolateral amygdala, and the relative lack of CCK-A receptors in such areas.\(^34,90\)

**CCK and reward-related behaviours**

It has long been known that the dopaminergic projections from the VTA to the NAcc are involved in positively motivated behaviours and natural rewarding behaviours such as feeding,\(^95,96\) sexual behaviour\(^94\) and locomotor activity.\(^95,96\) The mesoaccumbens DA pathway is also highly implicated in the primary rewarding effects of drugs of abuse\(^95\) and in the process of sensiti-
CCK receptor subtypes

Sensitization, in which subsequent presentations of a drug result in an increased neurochemical and behavioural response. Sensitization is thought to play an important role in the development of addictions. The colocalization of CCK with DA in this pathway suggests a functional role for CCK in reward behaviours. Furthermore, CCK-containing projections from the prefrontal cortex to the striatum, which also contain glutamate, may also play an important role in reward-related behaviours, given that glutamate has also been shown to be important in the induction and expression of sensitization.

CCK is colocalized with DA in most VTA cell bodies, and terminals containing both CCK and DA are present in the NAcc. One major CCK-ergic input of the accumbens originates in the substantia nigra pars compacta (SNc) and VTA. The rostral pole of the NAcc is equally innervated by CCK neurons projecting from both the SNc and the VTA, whereas the primary source of CCK innervation of the NAcc core is the SNc, and the primary source of CCK innervation of the shell region originates primarily in the VTA. Given the close anatomical links between CCK and DA in mesoaccumbens areas, it is reasonable to assume that CCK may play a modulatory role in this pathway and may modulate behaviours associated with mesolimbic DA function. Other, non-mesolimbic sources of CCK in the NAcc arise from projections from the cortex, especially the medial prefrontal cortex, and the amygdala.

The heterogeneity of CCK function in the NAcc has led to some seemingly contradictory results in the literature, and it is important to keep in mind that the neurochemical and behavioural effects of CCK on DA and DA-mediated behaviours vary depending upon the site within the NAcc that is being examined. For example, K⁺-stimulated DA release is potentiated by CCK in the caudal NAcc and inhibited by CCK in the rostral NAcc, and this is blocked by CCK-A antagonists in the caudal NAcc and CCK-B antagonists in the rostral NAcc.

In general, in the caudal shell area of the NAcc, CCK stimulation has DA agonistic-like effects, such as increased firing of DA neurons and increases in DA turnover (DOPAC and HVA). This effect is seen with CCK-8S but not with CCK-4 injections, suggesting that this effect is mediated by CCK-A receptors in the caudal shell of the Nacc. Conversely, CCK stimulation in the rostral core area of the NAcc has DA antagonistic effects, such as attenuated K⁺-stimulated DA release and decreased extracellular DA concentrations and turnover, which appear to be mediated by CCK-B receptors. The increase in DA release after amphetamine administration is attenuated by central injections of BOC-CCK-4 or CCK-8U and by central or systemic administration of CCK-8S. Therefore, it is likely that CCK-B receptors mediate the suppression by CCK of basal and augmented DA release in the rostral core of the NAcc. CCK-B receptor stimulation may also functionally oppose the postsynaptic effects of DA in the NAcc. These data indicate that CCK-A receptors are likely localized mostly in the caudal shell region of the NAcc, whereas CCK-B receptors are mostly localized in the rostral core in the NAcc.

Self-administration

The NAcc is highly implicated in drug self-administration and other incentive-driven behaviours. Drug self-administration in animals can be studied using both progressive-ratio and fixed-ratio schedules of reinforcement. In a fixed-ratio schedule, a predefined number of responses results in the delivery of a reinforcer. This schedule results in an inverted-U shaped dose–response curve, with lower drug doses increasing and higher drug doses decreasing responding. With the fixed-ratio schedule, it is difficult to interpret behaviour in motivational terms, and the rate of responding can be a confounding factor. The progressive-ratio schedule involves an exponentially increasing response requirement and is thought to more accurately reflect motivation to work for reward and the reinforcing effects of the drugs.

Intra-accumbens administration of the CCK-B agonist pentagastrin decreases break points on a progressive-ratio schedule for intravenous amphetamine self-administration, consistent with a neuroleptic-like or DA-antagonistic effect. Importantly, the same treatment increases responding on a fixed-ratio schedule of reinforcement, consistent with the effects of DA antagonists on fixed-ratio responding and demonstrating that the effects seen with the progressive-ratio schedule are not due to motor artifacts. CCK-B antagonists have also been shown to decrease cocaine drinking in cocaine-preferring rats in a free-choice model. CCK-A ligands have not been thoroughly examined in drug self-administration paradigms, although there is a suggestion that CCK-A antagonists may decrease
alcohol consumption in alcohol-preferring rats, but have no effect on cocaine intake.12

In general, these results suggest a role of NAcc CCK-B receptors in modulating acute psychostimulant self-administration.

**Sensitization**

CCK also plays an important role in psychostimulant sensitization, in which the locomotor response to the same dose of psychostimulant is increased after repeated drug administration. Sensitization is believed to be an important process in the initiation and development of drug addiction.100,101,133,134 In a typical sensitization paradigm, a psychostimulant is administered intermittently over days, and the sensitized response is measured after a brief (10–14 day) waiting period.135

Two distinct brain regions appear to be involved in the development and the expression of sensitization. The DA cell bodies of the VTA are critical in the development of sensitization, whereas the DA terminals in the NAcc are necessary for the expression of sensitization.99 Sensitization develops as a result of the immediate cellular and molecular events that occur after repeated drug administration (which eventually lead to permanent changes in neuronal function), whereas the expression of sensitization is the long-term consequence of the acute effects.99 CCK-B receptors, but not CCK-A receptors, have been shown to be involved in the development of sensitization,15 which suggests an important role of CCK-B receptors in the acute effects of psychostimulants. Conversely, CCK-A, but not CCK-B, antagonists attenuate the expression of amphetamine-induced sensitization,15,136 suggesting that CCK-A receptors may interact with the long-term neurochemical consequences of psychostimulants. Interestingly, the CCK-A antagonists devazepide and PD-140,158 do not affect baseline or acute amphetamine-induced hyperlocomotion11,28,86,87 but do affect locomotion in amphetamine-sensitized rats.137 Rats that lack the CCK-A receptor develop less behavioural sensitization to repeated cocaine than do normal rats.138 However, because these rats have been without CCK-A receptors throughout development, it is not possible to determine if this is due to a lack of induction or a lack of expression of sensitization. Rats that have been sensitized with cocaine show significantly higher basal and cocaine-induced extracellular CCK levels in the NAcc shell than non-sensitized rats,139 again indicating a role for CCK in sensitization. This increase in CCK could be of either cortical or mesolimbic origin. Regardless of the source, increased CCK in the shell would preferentially activate CCK-A receptors, which have DA facilitatory effects and thus would increase DA function. Increased DA in the shell of the NAcc is seen in cocaine-sensitized rats.140

The differential roles of CCK-A and CCK-B receptors in the development and expression of sensitization may be the result of neuroanatomical differences in receptor distribution or differences in the post-receptor events initiated by the 2 types of receptor. Further experimentation will be necessary to determine this.

Stress exposure is known to cross-sensitize with psychostimulant administration,99 and CCK-A antagonists also attenuate the exaggerated (sensitized) locomotor response to amphetamine in rats that have been chronically restrained.141 This finding further suggests that CCK may play a common modulatory role in both the response to chronic stress and the response to chronic psychostimulants. CCK-A receptors appear to be involved only in the expression of sensitized behaviour, however, and not in its development.

**Summary**

The findings indicate an important role of CCK-A and CCK-B receptors in different aspects of reward-related behaviour. CCK-B receptors in the NAcc appear to be important in modulating acute psychostimulant self-administration and the acute events surrounding the development of sensitization, whereas CCK-A receptors in the NAcc are important for the expression of locomotor sensitization to both chronic stressors and chronic psychostimulant administration. The role of CCK-A receptors in the expression of sensitization is consistent with their localization in the shell of the NAcc. The role of CCK-A receptors in the expression of sensitized locomotor behaviour is also consistent with the role of CCK-A receptors in facilitating DA function in the caudal shell region of the accumbens. These findings also illustrate that the effect of CCK antagonists is best seen under conditions of potentiated behaviour, such as during psychostimulant self-administration or psychostimulant-induced increases in behaviour.86,114,130,131,142,143

These findings are also consistent with the differential storage and release of coexisting classical and peptide neurotransmitters, in which peptide is coreleased predominantly under conditions associated with high
levels of release of the classical transmitter and elevated neuronal activity.\textsuperscript{14,15} Thus, only under potentiated conditions would CCK be released, whether from mesolimbic or corticostriatal projections, and only under these potentiated conditions would CCK-A or CCK-B antagonists be effective. The effects of CCK antagonists would not be readily detected under basal conditions, when CCK is not released.

**General conclusions**

This paper has reviewed the behavioural evidence regarding the roles of CCK-A and CCK-B receptors in anxiety-related behaviours and response to psycho-stimulants. The modulatory role of CCK in these behaviours has been emphasized and the differential role of CCK-A and CCK-B receptors noted.

There is considerable evidence that CCK-B receptors in the basolateral amygdala are capable of inducing anxiety when activated and that CCK-B receptor antagonists can reduce potentiated states of anxiety, but they do not have a large or consistent effect on non-potentiated or basal levels of anxiety. Thus, CCK-B receptors in the basolateral amygdala appear to play an important role in mediating the rapid, acute response to anxiety.\textsuperscript{8,14} At this time, there is not much evidence to implicate CCK-A receptors in the modulation of anxiety.

As might be expected from the colocalization of CCK and DA in the mesolimbic DA pathway, CCK does appear to play an important modulatory role in the behavioural and neurochemical response to psycho-stimulants. CCK appears to modulate both chronic and acute effects of psycho-stimulants, likely through the differential effects of CCK-A and CCK-B receptors, respectively. Activation of NAcc CCK-B receptors, located primarily in the rostral core portion of the NAcc, decreases the rewarding effects of reinforcing stimuli,\textsuperscript{7,9,10,11} and systemically administered CCK-B antagonists can affect the development of psycho-stimulant sensitization. Activation of CCK-A receptors in the caudal shell region of the NAcc has DA agonistic effects. This is seen experimentally by the attenuation of the expression of a sensitized locomotor response by CCK-A antagonists. The role of CCK-A receptors in psycho-stimulant self-administration has not been thoroughly examined to date.

In summary, the colocalization of CCK with classical neurotransmitters and the differential localization and function of CCK receptor subtypes allows for CCK to have modulatory influences on a wide variety of behavioural processes. CCK plays important neuro-modulatory roles in reward-related behaviours via mesolimbic DA influences, as well as in the control of anxiety-related behaviour via the amygdala. Understanding the differential localization and actions of CCK-A and CCK-B receptors and the recruitment of CCK only under potentiated behavioural states may help to clarify the past literature and guide future studies on the roles that this abundant and widely distributed neuropeptide plays in modulating behaviour.

**Competing interests:** None declared.

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**2002 Jock Cleghorn Prize**

**Ms. Richelle Booker** was the recipient of the 2002 Canadian College of Neuropsychopharmacology (CCNP) Jock Cleghorn Prize. Ms. Booker is doing research training in the Department of Psychiatry, University of Alberta in Edmonton. This award is designed to recognize the best poster presentation by a research trainee at the Annual Meeting of the CCNP. The award, donated by the CCNP, consists of $500. Congratulations to Ms. Booker!

**Presentation:** Inhibition of $^3$H-GABA uptake in rat brain cortical prisms by *Hypericum perforatum*, several of its constituents and a range of commercially available preparations.