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Abdeslem El Idrissi
William J. L'Amoreaux *Editors*

Taurine 8

Volume 1: The Nervous System, Immune System, Diabetes and the Cardiovascular System

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Volume 1: The Nervous System, Immune System, Diabetes and the Cardiovascular System

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Preface

The organizing committee wishes to thank all attendees of the 18th International Taurine Meeting that took place in Marrakesh, Morocco, from April 7th to 13th. This year, the conference highlighted the "*Mystique of Taurine*." Taurine investigators have had the privilege of attending these scientific meetings on three continents: Asia, Europe, and North America. This marked the first time that our conference was held in Africa. As a result, we present here the data from investigators from five of the six continents (sadly taurine research has yet to hit Antarctica). With this geographical expansion, the interest in taurine research has exponentially grown. This international meeting was attended by approximately 120 scientists. We present here information on the roles of taurine in a variety of organ systems, from the brain to the reproductive system and every system in between. As you are keenly aware, there is certainly a mystique to taurine. Is it beneficial or harmful? Does it protect cells or induce cell death? Can it be used in conjunction with another molecule to benefit health or cause death? The answer (or at least a hint to the answer) to these and other questions lies within this body of works. Of course, not all questions were answered but there were many discussions that generated numerous new ideas that will be taken home and tested in the laboratory.

This meeting was also unique in that many undergraduate and graduate students from the College of Staten Island/CUNY attended and presented their research as part of a study abroad program. This opportunity represented the first time that most of these students attended an international conference. More importantly, it served to stimulate interest in taurine research and recruit future taurine researchers. We are greatly appreciative for the overwhelming support of the College of Staten Island's administration, particularly Dr. Deborah Vess, Associate Provost for Undergraduate Studies and Academic Programs; Dr. William Fritz, the provost; Renee Cassidy, study abroad advisory from The Center for International Service; Debra Evans-Greene, Director of the Office of Access and Success Programs; and Dr. Claude Braithwaite of the City College of New York and the Louis Stokes Alliance for Minority Participation.

The abstracts of the conference were published in the journal "Amino Acids" (Vol. 42, Issue 4). We thank Drs. Lubec and Panuschka for making this possible.

Because of the success of this meeting, the organizing committee wishes to gratefully acknowledge the following:

- Taisho Pharmaceutical Co., Ltd., Tokyo Japan for their generous financial support.
- Professor Dr. Gert Lubec, FRSC (UK), Medical University of Vienna and Editor in Chief of AMINO ACIDS.
- Dr. Claudia Panuschka, Springer Wien, New York, Senior Editor Biomedicine/ Life Sciences.
- Dr. Portia E. Formento, Editor, Biomedicine, Springer US.
- Dr. Melanie Tucker (Wilichinsky) Editor, Genetics and Systems Biology, Springer US.

On behalf of the organizing committee, I thank all the attendees of the 18th international Taurine Meeting and the sponsors that made this meeting possible.

Staten Island, NY, USA Abdeslem El Idrissi

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Part I
Taurine and Its Actions on the Nervous System

Chapter 1
Neuropsychopharmacological Actions of Taurine

Shailesh P. Banerjee, Andre Ragnauth, Christopher Y. Chan, Mervan S. Agovic, Vincent Sostris, Iman Jashanmal, Louis Vidal, and Eitan Friedman

Abstract Taurine, an endogenous amino sulfonic acid, exhibits numerous neuropsychopharmacological activities. Previous studies in our laboratory have shown that it is an effective anti-cataleptic and neuro-protective agent. Current investigations show that acute or chronic administration of psychotropic drug cocaine may increase extracellular release of endogenous taurine which may protect

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against deleterious effects of the substances of abuse. Taurine administration was found to prevent cocaine-induced addiction by suppressing spontaneous locomotor activity and conditioned place preference. Taurine markedly delayed tail-flick response in rats which was significantly different from that in the group of animal receiving the same volume of saline, thereby indicating that taurine is a potentially valuable analgesic agent. Both taurine and endomorphin-1 were found to suppress the delayed broad negative evoked field potentials in anterior insular cortex (upper layer 5) by partially inhibiting NMDA receptor system. Thus, taurine is a unique psychopharmacological compound with potential for a variety of therapeutic uses including as a neuro-protective, anti-cataleptic, anti-addicting, and analgesic agent.

Abbreviations

NMDA	*N*-Methyl-D-aspartate
GABA	Gama-amino-butyric acid
APV	DL-2-Amino-5-phosphonopentanoic acid
CPP	Conditioned place preference

1.1 Introduction

We have focused our attention on the neuropsychological actions of taurine over the last several years. In this chapter, rather than trying to survey all known psychopharmacological activities of taurine, we will restrict our discussion to investigations conducted in our laboratories. Previously, we reported that therapeutic actions of typical and atypical antipsychotic drugs are mediated, in part, by partial agonistic activity on the NMDA receptor subtype glutamatergic transmission (Banerjee et al. 1995; Lidsky and Banerjee 1993, 1996; Lidsky et al. 1997). On the other hand, antipsychotic-induced side effects, such as catalepsy, were shown to occur as a result of complex changes in a variety of neurotransmitter functions, including glutamatergic and dopaminergic neuronal pathways in the striatum (Agovic et al. 2008). It was proposed that haloperidol-induced catalepsy occurs due to augmentation of NMDA-mediated glutamatergic transmission, inhibition of dopamine D_2 receptor-mediated transmission, and unchanged dopamine D_1 receptor-mediated transmission in the basal ganglia following chronic treatment of haloperidol (Agovic et al. 2008). In order to investigate if haloperidol-induced catalepsy is mediated by the degeneration of dopaminergic neurons and/or changes in dopamine- and glutamate-mediated transmissions, we studied the effects of chronic haloperidol administration on the dopaminergic neurons in the basal ganglia. Daily administration of haloperidol for 3 weeks caused a significant diminution of endogenous dopamine levels, and tyrosine hydroxylase activities as well as a significant increase in the densities of dopamine D_2 receptor in the basal ganglia (Lidsky et al. 1994 and Lidsky et al. 1995). These observations indicate that chronic haloperidol treatment may

cause degeneration of dopaminergic neurons in the basal ganglia as well as catalepsy. Interestingly, rats that were previously primed with a week of treatment of taurine and then given both haloperidol and taurine for 3 weeks, showed no development of catalepsy or significant changes in the levels of dopamine or tyrosine hydroxylase activities or in the dopamine D_2 receptor densities in the basal ganglia (Lidsky et al. 1995). Taurine therefore appears to prevent both haloperidol-induced neurodegeneration of dopamine neurons in the basal ganglia and the development of catalepsy in rats. The probable mechanisms for the neuro-protective and anti-cataleptic actions of taurine was proposed to be mediated by either its antagonism to glutamate-induced excitotoxicity and/or by its functioning as a partial agonist at the $GABA_A$ receptor (Quinn and Miller 1992). In another study, we found that both pre- and postnatal exposure to cocaine-induced neurotoxicity retards the development of dopamine neurons in the striatum. This was prevented by simultaneous administration of relatively high doses of the NMDA antagonist, clozapine (Lidsky and Banerjee 1992; Lidsky et al. 1993), suggesting that cocaine-induced neurotoxicity may occur due to the development of glutamate-mediated excitotoxicity (Yablonsky-Alter et al. 2005). Since exogenous taurine appears to oppose the neurotoxicity mediated by psychotropic drugs, we wondered whether endogenous taurine levels would be altered as a consequence of chronic substances of abuse exposure. Therefore, we measured extracellular taurine levels in the striatum following chronic cocaine treatment. Chronic cocaine administration significantly increased the extracellular levels of taurine in the striatum which further significantly increased following cocaine challenge to rats that previously had received chronic cocaine (Yablonsky-Alter et al. 2009). Therefore, it appears that endogenous taurine may oppose neurotoxicity induced by glutamate-mediated excitotoxicity, caused by the administration of exogenous psychotropic drugs. Taurine may open chloride channel through activation of a specific taurine receptor which is independent of $GABA_A$ or strychnine-sensitive glycine receptors to oppose glutamate-induced excitotoxicity (Yarbrough et al. 1981; Okamoto et al. 1983a, b). Alternatively, taurine may directly interact with the NMDA receptor to suppress its activity. This possibility was investigated by adopting electrophysiological and receptor binding studies. Taurine inhibited glutamate-induced evoked field potential that is mediated by NMDA receptor system in vitro in the rat prefrontal cortex in the presence of picrotoxin used to block the taurine and GABA-sensitive chloride channel. Also, taurine reduced by at least ten-fold, the apparent affinity of glycine, as well as partially inhibited the polyamine-activated calcium channel opening in NMDA receptor system as analyzed by measuring specific (^{3}H)-MK-801 binding to NMDA receptor in the rat cortical membrane preparations (Chan et al. 2012).

Thus, taurine may inhibit NMDA-mediated glutamatergic transmission by two independent mechanisms. First, it may open chloride channel on postsynaptic neurons to prevent depolarization and activation of NMDA receptor (Yarbrough et al. 1981; Okamoto et al. 1983a). Second, by interacting directly with the NMDA receptor system, taurine has been reported to partially inhibit APV-sensitive glutamate cell firing and polyamine-activated (^{3}H)MK-801 binding (Chan et al. 2012). Since a number of NMDA receptor antagonists have been shown to

exhibit a variety of neuropsychopharmacological activities, as exemplified by acamprosate showing anti-addicting action (Heilig and Egli 2006) and ketamine exhibiting antidepressant and analgesic actions (Autry et al. 2011; Sinner and Graf 2008), we decided to investigate possible neuropharmacological effects of taurine and these are described below.

1.2 Methods

1.2.1 Experimental Procedures

All the experimental procedures adopted in the current studies have been thoroughly described previously. Electrophysiological methods are described in another chapter by Chan et al. (2012). For this study, rat slices containing the rostral agranular insular cortex were prepared. Microdialysis assays to measure extracellular amino acids using high-pressure liquid chromatography (HPLC) have been previously described (Yablonsky-Alter et al. 2009). Extracellular dopamine levels were collected by microdialysis and quantified by using HPLC (Yablonsky-Alter et al. 2005). The methods for behavioral experiments including tail-flick test, spontaneous motor activity, and conditioned place preference have been previously described (Rodriguiz et al. 2008; Spinella et al. 1999; Ragnauth et al. 2000, 2001, 2005).

1.2.2 Statistic Analysis

Data were presented as mean ± S.E.M. Statistical significance of group means difference was measured by one-way analysis of variance (ANOVA), followed by Bonferroni's post hoc analysis. The threshold for statistical significance was assumed at $p < 0.05$. All statistical tests were calculated using GraphPad Prism (GraphPad Software, San Diego California, USA).

1.3 Results

1.3.1 Effects of Acute and Chronic Cocaine Treatment on Striatal Amino Acid Release

1.3.1.1 Effects of Acute Cocaine Treatment

The basal extracellular levels of glutamate, glycine, and taurine in striata of control rats were found to be similar in range (Fig. 1.1a). In contrast, the basal extracellular level of glutamine was approximately two to four times that of other three

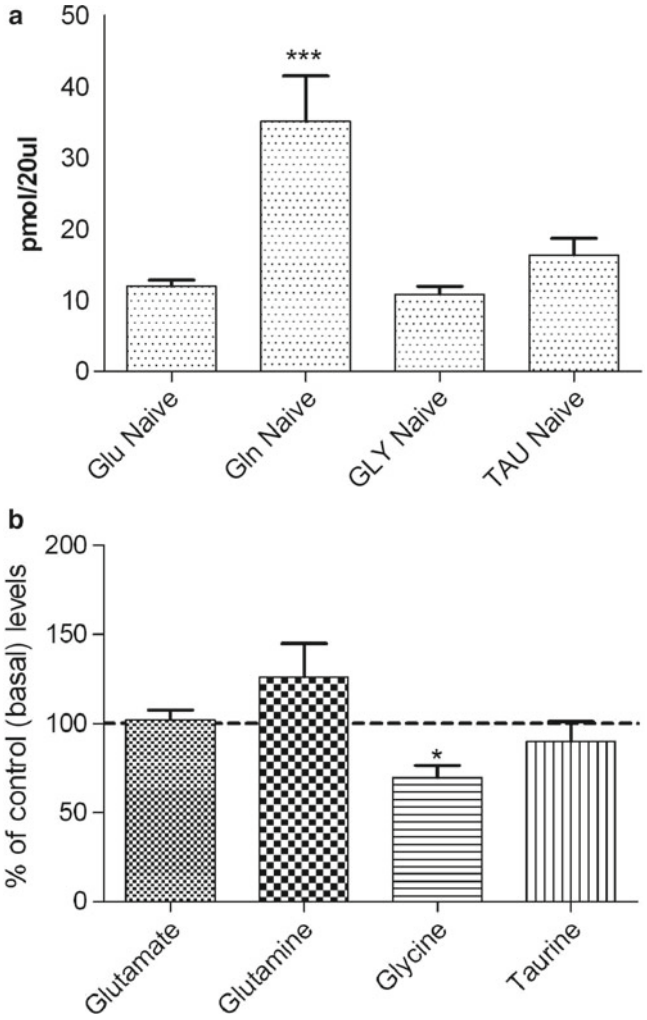

Fig. 1.1 Comparison of extracellular basal levels of glutamate, glutamine, glycine, and taurine in striata of (**a**) normal and (**b**) acute cocaine-treated rats. (**a**) Two groups consisted of six rats in each group. Control group received saline, while acute group received 10 mg/kg of intraperitoneal cocaine 30 min before microdialysis procedure. Glutamine in the control group was severalfold higher compared to other amino acids; no significant difference was observed between other amino acids. One-way ANOVA: $n = 6$; ***$p < 0.01$; Error bars, S.E.M. (**b**) Six, otherwise untreated rats were injected intraperitoneally with 10 mg/kg cocaine 30 min before the microdialysis collection. Only glycine extracellular concentrations were decreased significantly, while glutamine showed slight, not significant, increase. One-way ANOVA: $n = 6$; *$p = 0.0167$; Error bars, S.E.M

amino acids. Administration of 10 mg/kg of cocaine failed to alter the extracellular concentrations of glutamate and taurine (Fig. 1.1b). While acute cocaine significantly decreased the extracellular levels of glycine, it increased striatal extracellular levels of glutamine; however, this change was not statistically significant (Fig. 1.1b).

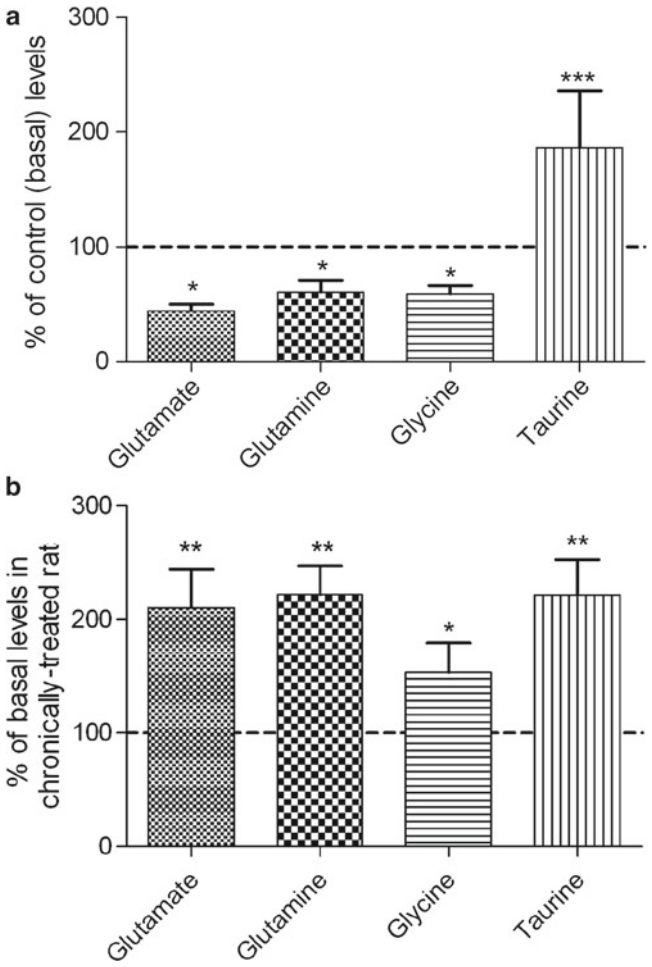

Fig. 1.2 Extracellular release of glutamate, glutamine, glycine, and taurine in striatum after (**a**) chronic cocaine treatment and (**b**) cocaine challenge to/in chronic cocaine-treated rats. (**a**) A group of six rats were injected intraperitoneally with 10 mg/kg cocaine, 6 days each week for 3 weeks and microdialysis was performed 24 h after the last injected dose. Compared to the control group (Fig 1.1a), there was a significant decrease in glutamate, glutamine, and glycine, while taurine was significantly increased. One-way ANOVA: $n=6$; *$p=0.3108$; ***$p=0.0020$; Error bars, S.E.M. (**b**) A group of six rats that was previously treated with cocaine for 3 weeks was challenged 24 h after the last dose with a single dose of 10 mg/kg cocaine, 30 min before microdialysis procedure. An increase in all four neurochemicals was recorded. One-way ANOVA: $n=6$; *$p=0.3108$; **$p<0.001$; Error bars, S.E.M

1.3.1.2 Effects of Chronic Cocaine Treatment on Basal Amino Acids Levels

The effects of chronic cocaine administration on basal extracellular concentrations of the four amino acids are shown in Fig. 1.2a. Basal extracellular concentrations of glutamate, glutamine, and glycine were significantly decreased as compared to basal

control levels, whereas, interestingly, the concentration of taurine was significantly increased when measured 24 h following the last daily injection of cocaine.

1.3.1.3 Effects of a Cocaine Challenge in Chronic Cocaine-Treated Rats

A single 10 mg/kg injection of cocaine given to rats which had previously received 3 weeks of chronic cocaine treatment, which was then withdrawn for 24 h, increased extracellular striatal levels of all amino acids including taurine (Fig. 1.2b).

In conclusion, potential cocaine-induced neurotoxicity following acute or chronic administration may be opposed by two separate endogenous mechanisms. First, acute effects are probably mitigated by diminution of glycine release that would reduce over-activation of NMDA receptor function. Second, chronic effects of the psychomotor stimulant may be opposed by endogenous release of taurine.

1.3.2 Effects of Taurine on Cocaine-Induced Locomotor Sensitization and Conditioned Place Preference

Additional endogenous taurine release in response to chronic cocaine treatment led to us to investigate whether pharmacological administration of taurine would prevent cocaine-induced addiction. This was tested by studying the effects of on cocaine-induced sensitization of locomotor activity and development of conditioned place preference (CPP). The effect of taurine on cocaine-induced augmentation of locomotor activity is shown in Fig. 1.3a. These results indicate that taurine is a suppressor of cocaine-induced locomotor sensitization, suggesting that it may oppose psychomotor stimulant's chronic effects including perhaps addiction. Next we investigated the influence of taurine on cocaine-induced place preference acquisition (Fig. 1.3b). Cocaine in a daily intraperitoneal (IP) dose of 15 mg/kg induced significant place preference acquisition after 8 days of habituation protocol. The psychomotor stimulant when co-administered with taurine failed to develop conditioned place preference. Thus, taurine may be effective in blocking cocaine-induced addiction.

1.3.3 Effect of Taurine on Tail-Flick Response in Rats

The NMDA receptor antagonist, ketamine, has been shown to be an effective analgesic agent and prevents hyperalgesia (Mathisen et al. 1995; Sinner and Graf 2008; Tverskoy et al. 1994). Therefore, we investigated the potential value of taurine in the management of pain by using tail-flick response in rats treated with either taurine or saline. Taurine (100 mg/kg) or equal volume of saline was administered IP for 9 days to rats before subjecting them to tail-flick tests. Taurine significantly delayed the tail-flick response as compared to saline-treated animals (Table 1.1),

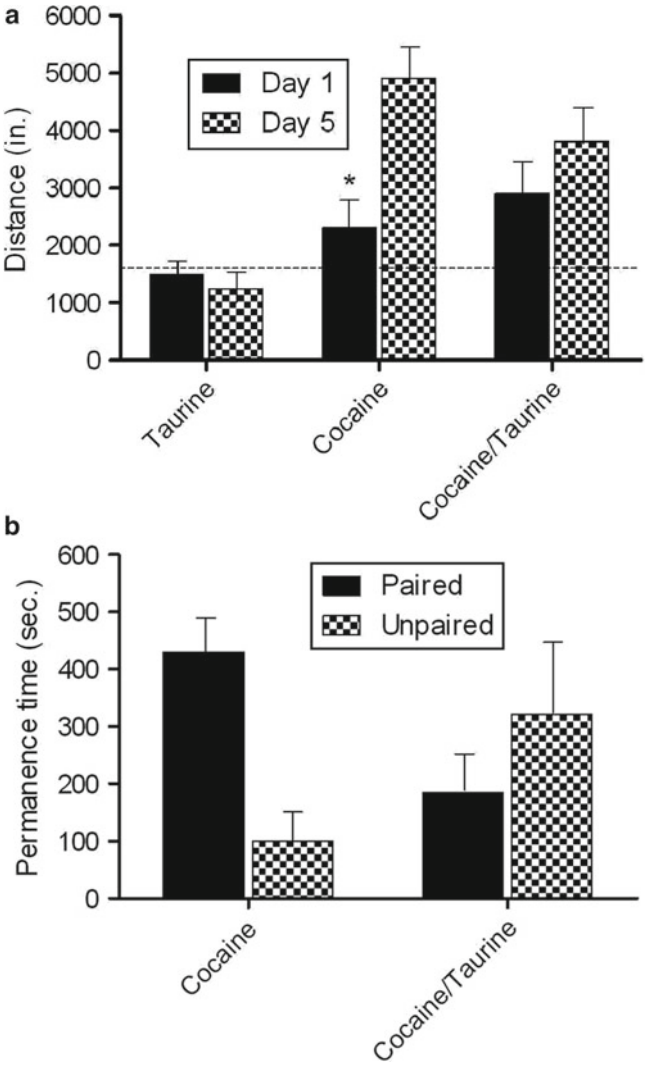

Fig. 1.3 (**a**) Effect of taurine on cocaine-induced locomotor sensitization. Average locomotion during habituation phase did not vary significantly between any of the groups tested and is indicated by the *dashed line*. Daily taurine injections (100 mg/kg) failed to induce significant sensitization after 5 days. When preceded by 7 days of daily 100 mg/kg of taurine preloading and daily injections of 15 mg/kg cocaine-induced sensitization as indicated by a significant increase in distance traveled at day 5 vs. day 1 (* = *t* test; $p < 0.05$). When co-administered with taurine (100 mg/kg), cocaine failed to induce significant sensitization in animals that were primed with taurine after 5 days. (**b**) Effect of taurine on cocaine-induced place preference acquisition. Cocaine (dose = 15 mg/kg) injections induced significant place preference acquisition following an 8 day habituation protocol (*t* test; $p < 0.05$). When preceded by 7 days of taurine (daily 100 mg/kg) preloading and co-administered with taurine (dose = 100 mg/kg), cocaine (dose = 15 mg/kg) failed to induce significant place preference acquisition

Table 1.1 Effect of taurine with and without naltrexone on tail-flick response

Condition	Mean tail-flick latency (s)	SE	Significance
Saline	11.32	±1.72	ns
Saline + NTX	10.76	±2.31	ns
Taurine	21.87	±1.62	s
Taurine + NTX	11.78	±3.07	ns

suggesting that it may be a useful analgesic agent. Interestingly, rats that received naltrexone (68 μg/kg) 15 min before the final dose of taurine showed no significant difference in the duration of time needed to exhibit tail-flick response as compared to saline- and naltrexone-treated animals (Table 1.1). The ability of naltrexone to at least partially block taurine-mediated analgesia indicates that taurine may relieve pain by activation of endogenous morphine pathways. Alternatively, opioids and taurine may diminish pain signals by the inhibition of glutamatergic transmission mediated by the NMDA receptor on CNS loci in pain pathways.

1.3.4 Effect of Taurine and Endomorphin-1 Glutamate Evoked Response in Anterior Insular Cortex

To seek support for the above possibility, we studied the effects of taurine and endomorphin-1 on evoked field potentials that were evoked in the upper layer-5 of rat rostral insular cortical slices by single pulses (0.04 Hz; 0.03 ms duration, 1.3× threshold current) delivered from concentric bipolar electrodes placed medial to the nucleus accumbens. Its response typically consisted of multiple wavelets, including a large negativity (Fig. 1.4), which is sensitive to the NMDA receptor antagonist APV (unpublished data). Bath application of either 2 mM taurine or 50 μM endomorphin-1 showed specific inhibition of this presumed NMDA-receptor-mediated response (Fig. 1.4a, b, respectively). These results indicate that both taurine and endomorphin-1 may induce analgesia by the inhibition of glutamate transmission mediated by the NMDA receptor. The precise mechanisms for taurine- or endomorphin-1-mediated inhibition of the NMDA receptor in the CNS pain pathway including the dorsal horn in the spinal cord remain to be elucidated.

1.4 Discussion

Taurine, which is an endogenous amino sulfonic acid, has been shown to be an inhibitory neuromodulator. Our previous studies have shown it to be an effective neuro-protective and anti-cataleptic agent (Lidsky et al. 1995). Taurine exhibits

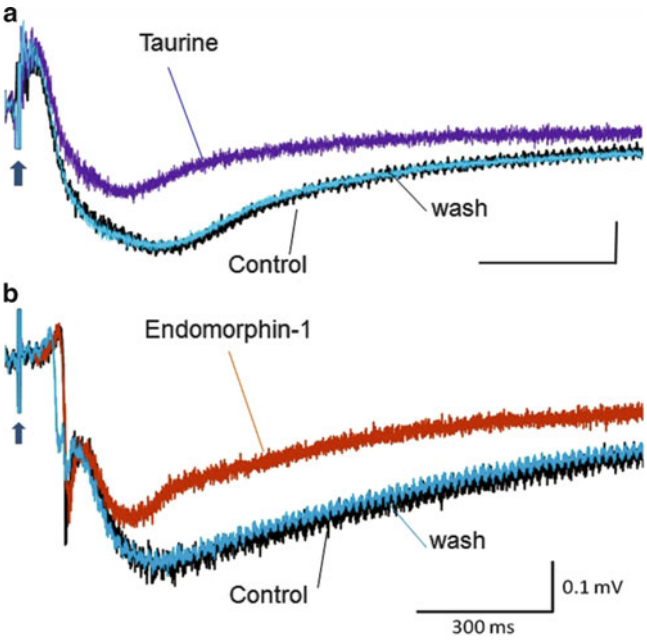

Fig. 1.4 Effect of taurine and of endomorphin-1 on NMDA-receptor-mediated evoked response in rat anterior insular cortical slices. (**a**) Superimposed upper layer-5 rostral agranular insular cortical field potential responses to ventral medial cortical stimulation by single electrical pulses (*arrow head*) recorded from a slice superfused with artificial cerebral spinal fluid (ACSF: control), 2 mM taurine, and ACSF wash. The taurine effect was restricted to the latter part of the negative wave, which is sensitive to NMDA receptor antagonists (unpublished data). (**b**) Experimental conditions were similar to those described in (**a**) except 50 nM endomorphine-1 instead of taurine was used. The endomorphine-1 effect was also mainly restricted to the latter part of the evoked response. Calibration scales for (**b**) apply to (**a**)

neuro-protection by physiological and pharmacological mechanisms. Chronic exposure to psychotropic drugs such as cocaine-induced body insult is opposed by additional extracellular release of taurine (Yablonsky-Alter et al. 2009; Fig. 1.2a). This may be considered as a physiological mechanism for counteracting the adverse effects of chronic intake of substances of abuse. Another possible physiological mechanism for protecting the central nervous system has been identified in this investigation. Acute administration of cocaine was found to suppress extracellular release of glycine (Fig. 1.1b). Since glycine is a co-transmitter with glutamate in the activation NMDA receptor (Lidsky and Banerjee 1993), diminution of extracellular glycine release would be expected to reduce glutamatergic transmission and subsequent possible excitotoxicity. Therefore, two separate physiological mechanisms may be available to counteract adverse effects of substances of abuse. The mechanisms for development for such counteractive protective mechanisms remain to be elucidated. Our and other studies indicate that an increase in either glutamate release or receptor sensitization may

often be associated with enhancement of taurine release, but how these different changes may be connected to each other is not known.

Although observed physiological mechanisms involving an extracellular increase in taurine and an extracellular decrease in glycine may potentially oppose deleterious effects of substances of abuse, these are not sufficient to prevent the development of addiction. Drug addiction, however, may be opposed and possibly prevented by taurine-mediated pharmacological mechanisms. Our studies show that cocaine-induced drug addiction as assessed by observing increase in locomotor activity and conditioned place preference may be prevented when animals are primed with taurine for several days followed by simultaneous chronic cocaine and additional taurine administration (Fig. 1.2a, b). Several mechanisms may be considered for pharmacological anti-addicting activity of taurine. Substances of abuse are believed to co-opt synaptic plasticity mechanisms in brain circuits that are involved in reinforcement and reward processing, as well as those which are responsible for learning and memory (Hyman et al. 2006). Although a variety of neuronal systems play a role in the development of addiction, dopamine is recognized to play a leading role in reinforcement and reward processes, while the glutamatergic system is involved in learning and memory (Kauer and Malenka 2007). Taurine may reduce glutamatergic activity by two separate mechanisms. First, taurine has been shown to open chloride channels which are independent of GABA and inhibitory glycine receptors to decrease depolarization state of the target cells (Yarbrough et al. 1981; Okamoto et al. 1983a, b). Second, taurine may directly interact at the glutamate NMDA receptor to suppress glutamatergic transmission (Chan et al. 2012). In addition, preliminary microdialysis studies in our laboratory show that chronic taurine treatment is effective in decreasing extracellular basal levels of dopamine, and it prevents acute cocaine-induced increase in the synaptic levels of dopamine in the nucleus accumbens (data not shown). Thus, taurine may interfere with dopamine-mediated reinforcing and rewarding processes to block drug addiction.

Pain stimuli are believed to originate in the primary afferent neuron at the periphery and then carried to the dorsal horn in the spinal cord, where it synapses with glutamate as well as other neuropeptide transmitters within the secondary neuron. Opioids have been shown to suppress release of glutamate and neuropeptides at the presynaptic sites in the dorsal horn and reverse or oppose postsynaptic depolarization by stimulating potassium efflux to attenuate transmission of pain signals (Schumacher et al. 2012). Clearly, NMDA receptor antagonists may exhibit analgesic activity, as has been shown for ketamine (Mathisen et al. 1995; Sinner and Graf 2008). Therefore, we wondered if taurine would function as a pain-relieving agent. Interestingly, in the tail-flick assay, taurine was found to be an effective analgesic agent (Table 1.1). Surprisingly, the opioid antagonist naltrexone markedly inhibited taurine-induced analgesia (Table 1.1), suggesting that either taurine may influence the opioid receptor system either directly or by co-opting its intracellular signaling mechanisms involved in opioid-induced analgesia. Notably, the NMDA receptor antagonist, ketamine, is known to enhance opioid-induced analgesia (Mathisen et al. 1995) and prevent hyperalgesia (Tverskoy et al. 1994), and ketamine has recently been shown to enhance the opioid-induced extracellular signal-regulated kinase 1/2 (ERK1/2) (Gupta et al. 2011). Since taurine

is a NMDA receptor antagonist (Chan et al. 2012) it is possible that taurine-mediated analgesic effect may be mediated by augmentation of ERK1/2 phosphorylation. Effects of taurine on opioid receptor system and opioid-induced ERK1/2 phosphorylation or mitogen-activated kinase are not known. Alternatively, taurine may not influence opioid receptor nor opioid-induced intracellular signaling, and it may, instead, potentiate endogenous opioid-induced inhibition of NMDA receptor activation by different independent mechanisms. Taurine has been shown to directly interactat the NMDA receptor complex to inhibit it at the postsynaptic site (Chan et al. 2012) and suppress glutamate release perhaps by opening chloride channel at the presynaptic site (Mochanova et al. 2007) to prevent depolarization at the presynaptic neurons.

Different mechanisms are involved in opioid-induced inhibition of glutamatergic transmission, such as opening of potassium channels at the postsynaptic site and closing of voltage-gated calcium channels at presynaptic site to suppress glutamate release (Fig. 1.5).

We propose that heat-induced pain leads to release of endogenous morphine peptides that may inhibit NMDA receptor system but fails to achieve the threshold level to cause prolongation of tail-flicking duration. The action of pre-administrated taurine either sums with or potentiates the inhibitory effect of endogenous opioids on the NMDA-receptor-induced response to raise the inhibition past the required level for inducing analgesia. By the same token, the observed reversal of this analgesic effect by naltrexone can be accounted for by a selective removal of the inhibition contributed by endogenous opioids such that the suprathreshold level of inhibition necessary for analgesia no longer exists (Table 1.1). Consistent with this hypothesis, we found that both taurine and endomorphin-1 inhibit glutamate-induced evoked response (Fig. 1.4a, b).

Finally, both opioids and taurine function as analgesic agents either share similar mechanisms or act by different modes of action to achieve the same goal of diminishing NMDA-mediated glutamatergic transmission. Taurine and opioids, however, exhibit opposite effects on drug-induced addiction. How do opioids cause addiction and how does taurine block this effect? It is believed that opioids disinhibit dopamine neurons in the ventral tegmental area by inhibiting GABA neurons at presynaptic site by preventing release of GABA through inhibition of voltage-gated calcium channels and postsynaptic site in dendrites by activating potassium channels to suppress depolarization (Fig. 1.6; Luscher 2012).

Disinhibition of dopamine neurons in the ventral tegmental area would be expected to stimulate dopamine release to reinforce reward system (Fig. 1.6; Hyman et al. 2006; Kauer and Malenka 2007). In contrast, taurine has been shown to suppress dopamine release in the nucleus accumbens by microdialysis in our laboratory (unpublished results). Thus, taurine opposes substances of abuse-induced drug addiction while opioids sustain it.

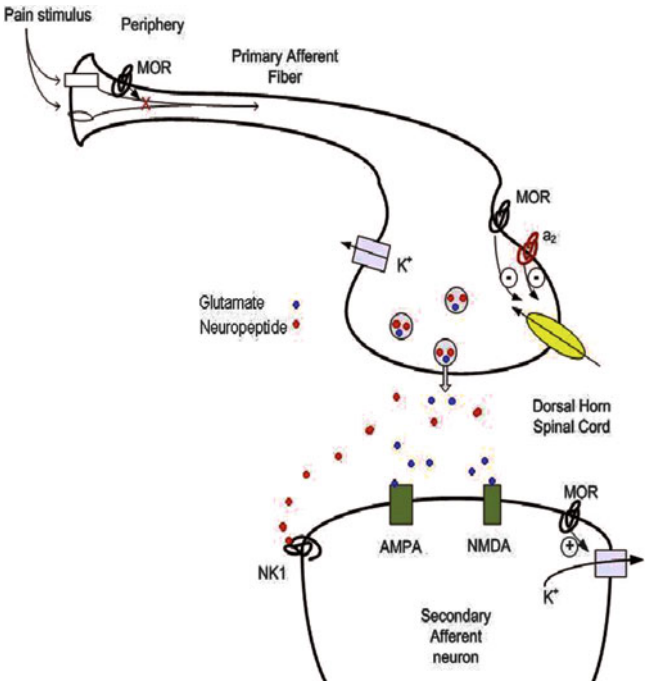

Fig. 1.5 Mechanisms for analgesic action of drugs mediated by the inhibition of glutamatergic transmission via NMDA receptor. The primary afferent neuronal pathway located in the periphery carries pain signals to the dorsal horn of the spinal cord, where it synapses with the secondary afferent neuron via glutamate and neuropeptide transmitters. An opioid agonist may inhibit the pain signal at the periphery or by its action at the dorsal horn cell. In the primary afferent neuron, it may inhibit voltage-gated calcium channel at the presynaptic site to suppress glutamate release and increase potassium efflux to diminish depolarization of the postsynaptic neuron to oppose activation of NMDA receptor and glutamatergic transmission. On the other hand, taurine may open the chloride channel at the presynaptic site to suppress release of glutamate and directly interacts with NMDA receptor at the postsynaptic site to inhibit glutamatergic transmission by different set of mechanisms than those utilized by opioids (Based on Schumacher et al. 2012)

1.5 Conclusion

Our investigations have identified diverse neuropsychopharmacological actions of taurine and these include neuro-protection, anti-cataleptic actions, anti-addiction actions, and analgesic activity. In addition, we found that endogenous taurine is released in the extracellular space perhaps to oppose harmful effects of substances of abuse.

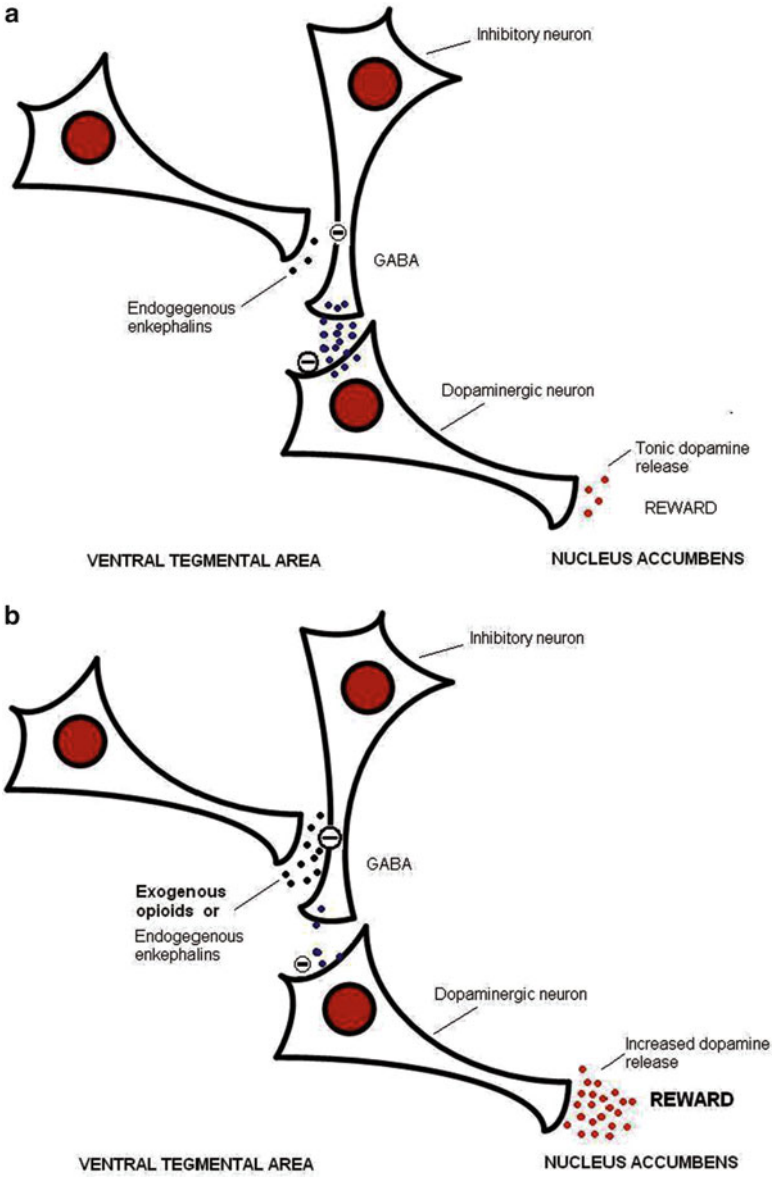

Fig. 1.6 Mechanisms for opioid-induced activation of the reward pathway. Dopaminergic neurons arising at the ventral tegmental area are believed to be involved in activating brain reward pathway in the nucleus accumbens and these are tonically inhibited by GABA interneurons. Opioids may inhibit GABA neuronal activity by suppressing GABA release to disinhibit dopaminergic neurons in activating the reward pathway. An opioid agonist may be either an endogenous substrate (**a**) or an exogenous drug (**b**). Interestingly taurine may have an opposite effect as unpublished studies in our laboratory indicate that taurine may suppress dopamine release in the nucleus accumbens, perhaps by opening chloride channel at the presynaptic site of dopaminergic neuron (Based on Martin et al. 2012)

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Chapter 2
Taurine and Its Neuroprotective Role

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Abstract Taurine plays multiple roles in the CNS including acting as a neuro-modulator, an osmoregulator, a regulator of cytoplasmic calcium levels, a trophic factor in development, and a neuroprotectant. In neurons taurine has been shown to prevent mitochondrial dysfunction and to protect against endoplasmic reticulum (ER) stress associated with neurological disorders. In cortical neurons in culture taurine protects against excitotoxicity through reversing an increase in levels of key ER signaling components including eIF-2-alpha and cleaved ATF6. The role of communication between the ER and mitochondrion is also important and examples are presented of protection by taurine against ER stress together with prevention of subsequent mitochondrial initiated apoptosis.

2.1 Introduction

Taurine, or 2-aminoethanesulfonic acid, is a sulfonic acid which is derived from cysteine and it is one of the few naturally occurring sulfonic acids. Taurine is widely distributed in animal tissues and one of the most abundant amino acid in mammals. Taurine plays several crucial roles including modulation of calcium signaling, osmoregulation, and membrane stabilization. However, despite extensive study, the mechanisms of action of taurine are not well understood. Based on past studies taurine has appeared as a promising agent for treating several neurological disorders including Alzheimer's disease, Huntington's disease, and stroke because of its ability to prevent apoptosis and its capacity to act as an antioxidant.

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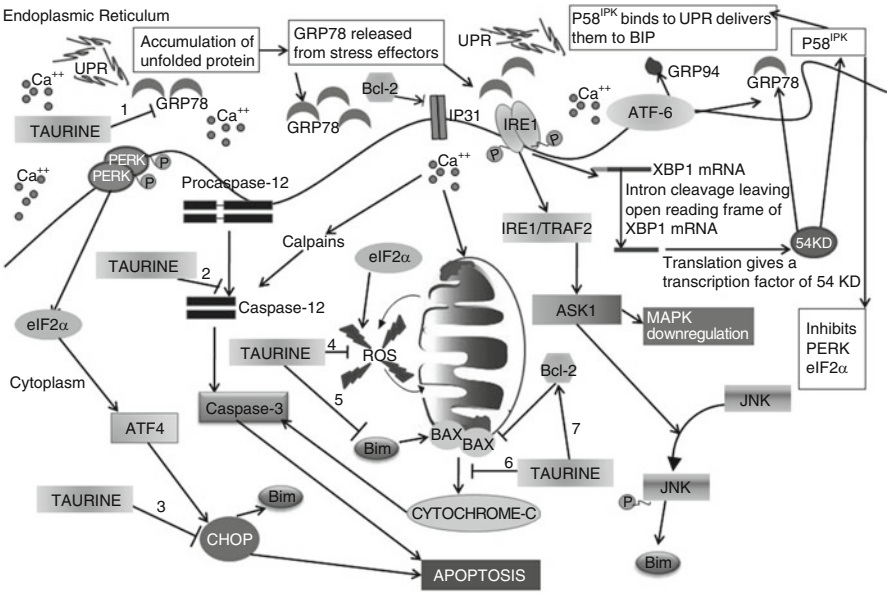

Fig. 2.1 Diagram showing the mode of action of taurine in alleviating the apoptosis induced by ER stress and mitochondrial dysfunction. The sites of action of taurine regulation are indicated a follows: (1) decreased Grp78, (2) decreased caspase 12, (3) decreased CHOP, (4) decreased ROS levels, (5) decreased Bim, (6) decreased cytochrome C release, and (7) increased Bcl-2

In this chapter, we will focus on the neuroprotective role of taurine. There has been extensive research demonstrating that taurine has a unique protective role and that it can downregulate several stress-associated proteins and increase neuronal survival under conditions of glutamate-induced cytotoxicity, mitochondrial stress, and endoplasmic reticulum (ER) stress (Fig. 2.1).

2.2 Taurine and Its Receptors

The taurine-synthesizing enzyme cysteine sulfinic acid decarboxylase (CSAD) in the brain was first identified and purified (Wu 1982) and then localized in the hippocampus (Taber et al. 1986), cerebellum (Chan-Palay et al. 1982b; Chan-Palay et al. 1982a), and the retina (Chan-Palay et al. 1982b; Chan-Palay et al. 1982a; Wu et al. 1985). Taurine fulfills most of the criteria as a neurotransmitter as the molecule is released from neurons in a calcium-dependent manner and binds to specific receptors postsynaptically (Lin et al. 1985a; Lin et al. 1985b; Wu and Prentice 2010; Wu et al. 1985). Taurine is of great interest as a potential neuroprotectant preventing excitotoxicity caused by glutamate which is a major excitatory neurotransmitter in the CNS. Part of the effect of taurine in neuroprotection involves