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Therapeutic potential of PACAP in alcohol toxicity

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ABSTRACT

Alcohol addiction is a worldwide concern as its detrimental effects go far beyond the addicted individual and can affect the entire family as well as the community. Considerable effort is being expended in understanding the neurobiological basis of such addiction in hope of developing effective prevention and/or intervention strategies. In addition, organ damage and neurotoxicological effects of alcohol are intensely investigated. Pharmacological approaches, so far, have only provided partial success in prevention or treatment of alcohol use disorder (AUD) including the neurotoxicological consequences of heavy drinking. Pituitary adenylate cyclase-activating polypeptide (PACAP) is an endogenous 38 amino-acid neuropeptide with demonstrated protection against neuronal injury, trauma as well as various endogenous and exogenous toxic agents including alcohol. In this mini-review, following a brief presentation of alcohol addiction and its neurotoxicity, the potential of PACAP as a therapeutic intervention in toxicological consequences of this devastating disorder is discussed.

1. Introduction

It is well established that high alcohol intake can result in alcoholism or alcohol use disorder (AUD), the latter being more commonly used terminology. Alcohol addiction develops over time and has a strong genetic component (Bell et al., 2016; Edenberg and Foroud, 2014; Reilly et al., 2017). Moreover, binge drinking in a naive individual where the blood alcohol concentration (BAC) may suddenly reach 400 mg% can result in fatal consequence preceded by unconsciousness and respiratory arrest (Collins and Neafsey, 2012; Su et al., 2017; Tizabi et al., 2018). Thus, at high BAC, clinically relevant neurotoxic effects reflected in mood disorders, cognitive and sleep impairments have been observed in human studies as well as in animal models (Broadwater et al., 2017; Liu and Crews, 2017; Miller et al., 2017; Sanchez-Marin et al., 2017). AUD can result in hypoactive prefrontal cortex leading to diminished executive functioning and hyperactive limbic system, leading to anxiety and negative emotion (Vetreno and Crews, 2014). Unfortunately, the few available pharmacological tools (discussed below) in combatting alcohol addiction do not present with desired efficacy and widespread application. In this review the potential of an endogenous peptide, pituitary adenylate cyclase-activating polypeptide (PACAP) in combatting the detrimental effects of alcohol, particularly on the central nervous system is discussed.

2. Clinical manifestations of alcoholism and treatments in humans

Although alcohol is a legal drug, it carries a significant risk of addiction in susceptible individuals, leading to AUD. It appears that AUD is more common than might have been imagined as in the United States alone, approximately 29% or 69 million people have experienced various degrees of AUD at some point in their lifetime. Within a 12-month period up to 14% or approximately 33 million people experience AUD. Majority (about 75%) of AUD arises from binge drinking (Grant et al., 2017). The most common symptoms are poor coordination, slurred speech, impaired cognitive functions (e.g. inability to think or remember properly), engaging in risky behavior and feeling powerless in controlling own drinking. Over time, depression, anxiety and insomnia may also be manifested (Oliveira et al., 2018; Tizabi et al., 2018). In contrast, withdrawal symptoms that can manifest as early as 2 h post drinking cessation include anxiety, shaking and in severe cases delirium tremens (DTs), which is associated with fever, tachycardia and confusion.

Long term alcohol use can also cause severe damage to other vital

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organs such as liver (e.g. liver cirrhosis, Mellinger and Winder, 2019), heart (e.g. arrhythmia, hypertension, cardiomyopathy, Mirijello et al., 2017), kidney (Varga et al., 2017), stomach (e.g. ulcers and gastritis, Bode and Bode, 1997) as well as metabolic syndrome (Vancampfort et al., 2016). The damaging effects of alcohol on the brain can be from a direct effect of alcohol on neurons, resulting in neuronal death or indirect through induction of vitamin B1 deficiency (Beriberi) that can lead to Wernicke-Korsakoff symptom (WKS). Prominent features of WKS include double vision, ptosis (drooping of upper eyelid), ataxia or loss of muscle coordination, confused mental state leading to violent behavior, learning and memory impairment, hallucination and confabulation (Moerman-van den Brink et al., 2018).

3. Pharmacological interventions in alcoholism

Few pharmacological tools are currently available to combat alcoholism. These include disulfiram, an acetaldehyde dehydrogenase inhibitor that induces aversion; naltrexone, an opioid antagonist that blunts the rewarding effects of alcohol, and acamprosate, a synthetic gamma amino butyric acid (GABA) analog that may act as a functional NMDA (N-methyl-D-Aspartate) receptor antagonist (Popp and Lovinger, 2000; Rammes et al., 2001), all of which are only modestly effective (Leggio and Addolorato, 2010; Zindel and Kranzler, 2014). Hence, significant effort is expended towards findings new targets.

4. Alcoholism, neurochemical consequences

Addiction to alcohol or any drug of abuse can be formed as a result of initial pleasure seeking and/or escape from stressful events. However, once addiction is initiated the reason for the continuation of drug seeking may be primarily to avoid withdrawal effects, which is also referred to as "the dark side" (Koob and Volkow, 2016). Regardless of the etiology, high alcohol intake can affect a variety of neurotransmitter systems as well as cellular mechanisms involved in neuronal plasticity and neuroinflammatory responses. In regard to the neurotransmitter systems, it is believed that alcohol interacts with all neurotransmitters including dopamine, serotonin, GABA, glutamate and acetylcholine. This is despite the fact that no specific receptor for alcohol has been identified. Yet, alcohol's interaction with these transmitter systems as well as neurotrophic and inflammatory factors (discussed below) is believed to be responsible for the various behavioral effects that were detailed above. Alcohol's interaction with glutamate and dopamine for example may play an important role in its addictive or reinforcing properties (Alasmari et al., 2018). Its interaction with the serotonergic-corticotropin-releasing factor may be associated with its induction of anxiety and depression (Forster et al., 2018; Pleil and Skelly, 2018); its interaction with GABA may have a pivotal role in the modulation of developmental plasticity (Granato and Dering, 2018) and its interaction with acetylcholine, particularly the nicotinic cholinergic system may be critical in alcohol's reward, dependence and mood related effects (Wu et al., 2014; Rahman, 2015), co-morbid drinking-smoking conditions (Meyerhoff et al., 2006; Kalejaiye et al., 2013), as well as in alcohol inflammatory response (Kalejaiye et al., 2017).

It has been hypothesized that alcohol-induced reduction of neurotrophic factors including brain-derived neurotrophic factor (BDNF) and elevation of inflammatory markers such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α in discrete brain regions may be the cause of mood, cognitive and sleep impairments in AUD (Tizabi et al., 2018). Furthermore, co-morbid manifestation of alcoholism and depression poses treatment challenges as the efficacy of the antidepressants may be compromised by alcohol consumption (Becker et al., 2017).

It is of relevance to note that an elevation in pro-inflammatory cytokines can cause a reduction in neurogenesis, indicating an inverse relationship between neurotrophic factors and pro-inflammatory cytokines (Felger and Lotrich, 2013; Ogłodek et al., 2014; Stepanichev et al., 2014). Moreover, alcohol-induced neuro-inflammation, in addition to causing various symptoms including depression, may also contribute to further alcohol-drinking behavior (Crews et al., 2017; de Timary et al., 2017; Hurley and Tizabi, 2013).

5. Alcoholism: neurotoxicological consequences

Neurotoxic effects of high alcohol concentration are also well confirmed in a variety of cell culture and slice preparation as reflected in damaging effects of alcohol on primary cortical and cerebellar neurons (Tizabi et al., 2004, 2005), on developing or developed hippocampal neurons (Gerace et al., 2016; Tomasini et al., 2016), on neuroblastoma-derived SH-SY5Y cells (Ramlochansingh et al., 2011), PC12 cells (Fang et al., 2016; Kumar et al., 2015) and organotypic slices (Collins et al., 2014; Lutz et al., 2015). A number of mechanisms for the cellular toxicity of alcohol have been proposed. These include, oxidative stress (Collins and Neafsey, 2012; Moon et al., 2014), enhanced apoptosis (Ieraci and Herrera, 2018), increase in inflammatory mediators (de Timary et al., 2017; Heberlein et al., 2014; Neupane et al., 2014), lipid membrane impairment and induction of edema (Collins, 2015; Kondela et al., 2017) and heat shock proteins (Mandrekar et al., 2008). Interestingly, some of the toxicity induced by alcohol might be largely due to acetaldehyde, a major alcohol metabolite, which is associated with formation of reactive oxygen and nitrogen species, impairment of energy homeostasis and depletion of important co-factors such as NAD+ (Rusyn and Bataller, 2013).

6. PACAP: neuroprotective potential

PACAP was first isolated in 1989 as a neuropeptide that stimulates cyclic AMP in pituitary cells (Miyata et al., 1989). PACAP belongs to the vasoactive intestinal peptide (VIP)/secretin/glucagon peptide family and exists in two amino-acid forms, PACAP38 and PACAP27. PACAP acts via G-protein coupled receptors, the specific PAC1 receptor with several splice variants and the VPAC1 and VPAC2 receptors that also bind VIP with similar affinity (Hirabayashi et al., 2018; Vaudry et al., 2009). In addition, transactivation of growth factor receptors, direct cellular uptake of the peptide and receptor internalization may account for the diverse effects of PACAP (Doan et al., 2012; Holighaus et al., 2011; Liao et al., 2018; Parsons and May, 2018). PACAP is a potent neurotrophic and neuroprotective peptide proven in various in vitro and in vivo models (Atlasz et al., 2018; Brifault et al., 2016; Manecka et al., 2016; Shioda et al., 2016; Watanabe et al., 2016). PACAP has proven to be a potent neuro- and cyto-protective peptide due to its antiapoptotic, anti-inflammatory and antioxidant effects (Abad and Tan, 2018; Reglodi et al., 2017, 2018b; Shioda et al., 2018). In this review, we concentrate mainly on PACAP's interaction with alcohol and its potential in reducing alcohol toxicity.

7. PACAP and alcohol addiction

PACAP and its receptors are expressed in the entire brain, including the limbic and other areas regulating various behaviors (Gupta et al., 2018; Roman et al., 2014; Vaudry et al., 2009; Vereczki et al., 2006). Functional studies have shown that PACAP signaling is involved in a variety of conditions such as stress, anxiety, fear, depression and cognitive functions (Iemolo et al., 2015; Jiang and Eiden, 2016; Miles et al., 2018; Mustafa et al., 2015; Roman et al., 2014). Also, PACAP and PAC1 receptor have been shown to be critical mediators of abnormal fear responses in rodents and in humans, which can lead to psychiatric disorders including posttraumatic stress disorder (PTSD) (Lebois and Ressler, 2016; Pohlack et al., 2015; Ramikie and Ressler, 2016). Indeed, some studies suggest that PACAP gene polymorphism might be associated with disorders such as schizophrenia and PTSD (Hashimoto et al., 2007; Lind et al., 2017; Mercer et al., 2016; Ressler et al., 2011). Similarly, PACAP polymorphism in humans and its dysregulation may

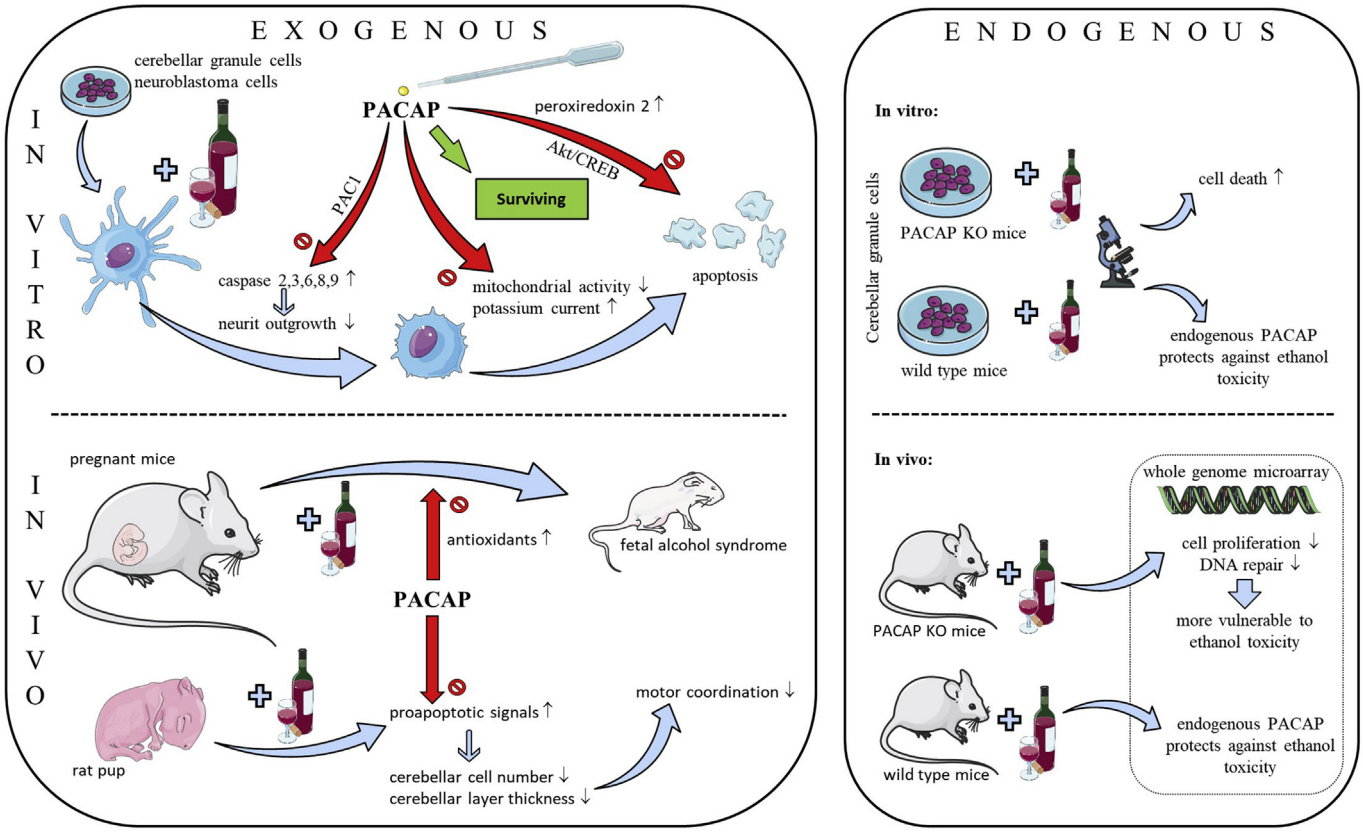

Fig. 1. PACAP protection against ethanol-induced toxicity in vitro and in vivo. Left panel describes survival-promoting effects of PACAP given as exogenous treatment in vitro (upper part) and in vivo (lower part), while on the right side effects on endogenous PACAP are summarized.
(Graphics are adapted from Servier Medical Art under a Creative Commons Attribution 3.0 Unported License.)

lead to major depressive disorders (Hashimoto et al., 2010; Tohyama et al., 2015). Rodent studies also confirm that PACAP deficient mice display a variety of behavioral abnormalities, including predisposition to depression-like phenotype (Farkas et al., 2017a; Hashimoto et al., 2009; Kormos et al., 2016), hyperactivity with explosive jumping behavior (Hashimoto et al., 2001), altered novelty seeking behavior (Hashimoto et al., 2001), deficit in prepulse inhibition (Tanaka et al., 2006) as well as some somatic developmental changes (Farkas et al., 2017b; Sandor et al., 2016; Watanabe et al., 2016).

PACAP/PAC1 receptor-induced pathways have also been implicated in addictive behavior (Mai et al., 2018; Miles et al., 2018). For example, administration of PACAP or the PAC1 receptor-specific agonist maxadilan in the bed nucleus of stria terminalis (BNST) can facilitate relapse following extinction of cocaine-seeking behavior (Miles et al., 2018). Moreover, a recent study has shown that PACAP signaling is involved in the interleukin-6-mediated neuronal responses to cocaine-induced kindling behaviors (Mai et al., 2018). Expression of PACAP/PACAP receptors has also been shown to be influenced by alcohol. In this regard, it has recently been reported that alcohol drinking in rats leads to an increase in PACAP gene expression and in levels of PACAP27 in individual cells of the paraventricular nucleus of the hypothalamus (Gupta et al., 2018). Alcohol-induced increase in PAC1 receptor mRNA is mediated through nuclear RACK1 transduction mechanism (He et al., 2002). More importantly, a role for PACAP/PAC1 system in alcohol addiction is supported by finding of an association between PACAP gene polymorphism and problematic alcohol use in a recent study involving nearly 500 young women (Dragan et al., 2017). Animal studies also confirm that PACAP-deficient mice have an increased preference towards alcohol (Tanaka et al., 2010). However, at this juncture direct involvement of PACAP in alcohol addiction and possible use of this peptide in prevention of alcoholism or its relapse remains unresolved.

8. PACAP protection against alcohol-induced toxicity in-vitro

The first results showing that PACAP reduces alcohol-induced cell toxicity came from cerebellar granule cells. In the cerebellum, PACAP has important developmental effects (Galas et al., 2017) and the neuropeptide's protective effects against alcohol, oxidative stress and ceramide in these cells have been amply documented (Brifault et al., 2016; Falluel-Morel et al., 2008; Manecka et al., 2016; Reglodi et al., 2018b; Vaudry et al., 2002a,b). Thus, co-treatment of granule cells with PACAP and ethanol (100 mM) for 24 h dose-dependently increased the number of surviving neurons, with a complete reversal of alcohol-induced toxicity. This was in contrast to VIP, which had no effect at similar concentrations, indicating that PACAP is acting primarily through PAC1 receptor (Vaudry et al., 2002b). PACAP treatment also restored the typical shape of differentiated neurons, opposing the effects of alcohol on cell shrinkage, nuclear condensation and neurite outgrowth (Vaudry et al., 2002b). In a later study, Vaudry and coworkers (2005) demonstrated that cultured cerebellar granule cells isolated from PACAP deficient mice react to the toxicity of alcohol with increased sensitivity. Thus, cell death in response to alcohol was much higher in cells derived from PACAP deficient mice compared to those isolated from wild type mice, suggesting that endogenous PACAP may provide protective effects against alcohol toxicity (Vaudry et al., 2005).

Regarding the mechanism of action, it was found that PACAP decreased alcohol-induced activation of caspases 2, 3, 6, 8 and 9, all of which are mediated through cAMP/PKA pathway. Subsequent studies by Castel and coworkers found that PACAP may also act via inhibition of potassium currents (Castel et al., 2006; Mei et al., 2004), while another study confirmed involvement of peroxiredoxin 2, an antioxidant enzyme, in protective effects of PACAP against alcohol toxicity (Botia et al., 2008). PACAP can also restore alcohol-induced decreases in

mitochondrial activity (Botia et al., 2008). Thus, several mechanisms of action for neuroprotective effects of PACAP are indicated. Interestingly, PACAP could induce these protective effects against alcohol not only as simultaneous treatment, but even when administered up to 6 h after alcohol administration (Vaudry et al., 2002b).

We have also reported on protective effects of PACAP against salsolinol-induced toxicity in neuroblastoma (SH-SY5Y) cells (Brown et al., 2013). Salsolinol is an endogenous compound that is derived from condensation of dopamine and aldehydes and in high levels can be selectively toxic to substantia nigra neurons (Możdżeń et al., 2015; Qualls et al., 2014). PACAP also has protective effects against inflammatory-mediated damage in these cells, via inhibiting caspase activation and stimulating CREB phosphorylation as well as BDNF expression (Brown et al., 2014). Recently, we showed that PACAP can also protect against toxicity induced by alcohol, nicotine or their combination in SH-SY5Y cells (Manavalan et al., 2017). These toxicities could be blocked by the PACAP antagonist PACAP6-38, suggesting involvement of the PAC1 receptor (Brown et al., 2014; Manavalan et al., 2017). Interestingly, the toxicity induced by the combination of low alcohol and nicotine concentrations appears to be due to increased influx of calcium into the cells, which is also ameliorated by PACAP application (Manavalan et al., 2017) (Fig. 1).

9. PACAP protection against alcohol-induced toxicity in-vivo

In-vivo studies have reinforced the in-vitro protective efficacy of PACAP against alcohol-induced toxicity (Botia et al., 2011) (Fig. 1). Fetal alcohol syndrome (FAS), including impairments in motor coordination modeled in 8-day-old rat pups, was significantly reduced by PACAP treatment (Botia et al., 2011). Studying the protective mechanism revealed that PACAP counteracted the increases in pro-apoptotic c-jun and bax, and the decrease in c-fos and bcl2. These factors involved in mitochondrial apoptotic pathway, finally lead to increased caspase activity, which was abrogated by PACAP both at mRNA and at protein activation levels (Botia et al., 2011). Moreover, PACAP ameliorated the marked reduction in the thickness of the cerebellar layers induced by alcohol, in a layer-specific manner (Botia et al., 2011). Together, these data point to the potential of PACAP in reversing alcohol-induced toxicity in the developing cerebellum, reflecting a FAS model (Botia et al., 2011). More recently, it was shown that PACAP prevented alcohol-induced reduction of body weight and brain atrophy in another model of FAS (Shili et al., 2017). In the latter model pregnant mice were treated with alcohol between gestational days 7–16 or 7 to 18, resembling human exposure that results in FAS (Shili et al., 2017). The authors reported that PACAP inhibited reactive oxygen species while preventing the decrease in antioxidant enzyme levels (superoxide dismutase and catalase), resulting in a reduction in lipid oxidation products. In addition, the FAS-induced behaviors of the pups tested 30 days after birth were markedly attenuated by PACAP. Thus, PACAP is able to counteract many of the deleterious effects of FAS (Botia et al., 2011; Shili et al., 2017).

10. Endogenous PACAP and protection against alcohol-induced toxicity

Given the strong survival-promoting effect of PACAP, it is not surprising that PACAP-deficient mice are more vulnerable to stressors, including alcohol. Indeed, as reported by numerous studies, PACAP deficient mice have been shown to respond to stressors with an increased injury (Reglodi et al., 2012). Thus, PACAP deficient mice have increased infarct volume in a stroke model (Ohtaki et al., 2006), more destruction in retinal layers in a model of retinal ischemia (Szabadfi et al., 2012) or retinal excitotoxicity (Endo et al., 2011), develop accelerated aging symptoms (Reglodi et al., 2018a,c; Kovács-Valasek et al., 2017) and more severe and prolonged encephalitis in a multiple sclerosis model (Van et al., 2018). In the periphery, mice lacking endogenous PACAP have impaired nerve regeneration (Watson et al., 2013) and altered fecal microbiota composition with virtually absent bifidobacteria as a major hallmark that might be linked to increased susceptibility to various diseases (Heimesaat et al., 2017). In fact, peripheral organs in PACAP-deficient animals also react with increased sensitivity to a variety of insults, such as intestinal and kidney ischemia (Ferencz et al., 2010; Laszlo et al., 2015), oxazolon-induced dermatitis (Kemény et al., 2010), dextran-induced colitis (Nemetz et al., 2008), doxorubicin-induced cardiomyopathy (Mori et al., 2010), endotoxin-induced subacute airway inflammation (Elekes et al., 2011) and demonstrate impaired corneal wound healing (Nakamachi et al., 2016).

Direct connection between alcohol toxicity and PACAP were demonstrated in PACAP knockout mice where the sedative-hypnotic effects as well as hypothermia induced by alcohol were significantly reduced in these mice (Tanaka et al., 2004). Alcohol sensitivity in PACAP mutant animals seems to be a phylogenetically conserved mechanism, as a similar phenomenon is observed in Drosophila (Hashimoto et al., 2002). Interestingly, however, PAC1 receptor deficient mice do not display enhanced sensitivity towards alcohol, but share other symptoms of PACAP deficiency such as hyper-locomotion and alterations in anxiety (Otto et al., 2001). Moreover, blood alcohol levels were not different between wild type and PACAP deficient mice at different time points following alcohol injection, indicating that PACAP does not influence alcohol metabolism (Tanaka et al., 2004).

In vivo studies in adolescent and adult mice have also revealed similar protective effects of PACAP against alcohol-induced toxicity (Lacaille et al., 2017), (Fig. 1). Thus, when adolescent and adult wild type and PACAP knockout (KO) mice were injected with alcohol in a binge drinking manner, only PACAP deficient mice had increased caspase-3 activity and reactive oxygen species production. Cell proliferation was also decreased in PACAP KO mice. Moreover, whole genome microarray analysis revealed that different sets of genes were affected in PACAP KO mice. In particular, genes associated with DNA repair and cell cycle were more affected in the KO mice (Lacaille et al., 2017). Taken together with other in-vivo studies it may be suggested that endogenous PACAP protects against alcohol toxicity not only during early development, but also during adolescent and adult age.

11. Concluding remarks

Alcohol induced toxicity either in form of FAS or other toxicological manifestation during adolescent and adulthood can have devastating consequences. PACAP, an endogenous peptide provides protection against various toxicants including alcohol. Hence, PACAP receptor activating compounds have therapeutic potential in counteracting alcohol-induced toxicity. Further research is needed to elucidate possible exploitation of this peptide in alcohol addiction itself.

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