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Review

Neuropeptide Y (NPY) in alcohol intake and dependence

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ABSTRACT

Neuropeptide Y has a role in alcohol intake and dependence. NPY's effect on alcohol intake appears to be in part dependent on the individual's history of alcohol dependence. In models of high intake such as alcohol-preferring, selectively bred rat lines (e.g., the P-line and the HAD line), as well as in ethanol-vapor-exposed subjects, NPY modulates alcohol intake while leaving it unaffected during baseline conditions. The primary receptor subtype mediating NPY's effect on ethanol intake remains in question. The Y2-antagonist BIIE0246 significantly suppresses ethanol intake in an operant paradigm with a sensitization to the effect of BIIE0246 in vapor-exposed subjects. We propose the NPY system to be one of the most interesting target systems for the development of treatments for alcohol abuse and dependence.

Contents

1. NPY in anxiety-related behavior

Neuropeptide Y (NPY) has been shown to have effects on emotional behavior and alcohol intake using rodent models. Anti-anxiety and sedative effects of exogenous NPY were early findings, and have since been shown in numerous animal studies. Icv administration of NPY to a large extent prevents gastric ulceration induced by a strong stressor, water restraint [12], and the anxiolytic properties of NPY have been demonstrated in a number of animal models of anxiety-related behavior, including the elevated plus-maze [3,13], social interaction task [28], fear potentiated startle and fear conditioned responses [3,10]. In addition, transgenic rats over-expressing NPY in hippocampus were shown to be resistant to stress-induced increases in anxiety-like behavior [5,33]. These studies together indicate that pharmacological or transgenic activation of NPY signaling reduces stress. The involvement of NPY in modulation of stress-responses, more

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specifically its anti-stress action, is supported by the finding that icv administration of the peptide produces synchronization of electroencephalogram activity, an effect mimicking that of sedatives and anxiolytic compounds such as benzodiazepines, and also decreases locomotor activity in rats [8,11]. Furthermore, expression of NPY in brain regions mediating stress-responses is differentially regulated by acute and repeated stress [32,37]. On the basis of these pharmacological and expression studies, it was proposed that an up-regulation of NPY expression may contribute to successful behavioral adaptation to stress, a concept extending a previously introduced hypothesis that NPY may act to ''buffer'' behavioral effects of stress-promoting signals such as CRF [14].

2. NPY and depression

There is increasing evidence, preclinical and clinical, pointing to an involvement of NPY in mood disorders such as depression. Depression-like states are accompanied by changes in NPY expression and an established anti-depressive treatment, electroconvulsive shock (ECS), has been consistent in up-regulating brain NPY-levels, with the hippocampus as a seemingly central target. An elevated NPY level was demonstrated after repeated but not single ECS, an effect mirroring the requirements for clinical effect in depressed subjects [15,16,21,22,38]. The mechanism is an up-regulation of preproNPY expression which leads to an increased extracellular availability of the NPY peptide. Against the background of our behavioral findings in the transgenic rat model [33], up-regulated hippocampal NPY-expression might be of importance for both therapeutic and amnesic effects of ECS. This would be in agreement with the finding that chronic cocaine use reduces NPY expression in the prefrontal cortex [39], since clinical hallmarks of cocaine withdrawal and dependence are symptoms of depression.

3. NPY in regulation of alcohol intake

The effect profile of NPY shows numerous similarities with not only that of established anti-anxiety compounds, but also that of alcohol. The results from anxiety and depression studies indicate that in addition to involvement in mood disorders such as depression and anxiety syndromes, NPY has a role in alcohol intake, dependence, and withdrawal. Furthermore, clinical studies of alcohol dependence show a correlation between initial anxiety and subsequent alcohol abuse, possibly due to the anxiolytic action of alcohol [23,24]. While this correlation may only be true for a subgroup of alcoholics, it may partially explain some of the changes and effects seen for NPY in alcoholism.

A direct link between NPY signaling and regulation of alcohol consumption was first shown in a study where mice with a transgenic overexpression of NPY consumed less alcohol, while mice with a null-mutation, i.e. inactivation, in the NPY gene had increased alcohol consumption [31]. Furthermore, differences in electrophysiological response to NPY [6] as well as differences in NPY expression in rat strains selected for high and low alcohol preference [7,17] were demonstrated. Taken together these findings lead to speculations that NPY may also be involved in regulation of alcohol dependence.

4. NPY and alcohol intake in animals with a history of dependence

Initially seemingly conflicting results were obtained when alcohol intake and preference were examined following central administration of NPY. A reduction in intake was seen in the preferring P-line [2] while studies in other strains using icv and localized administration yielded unaffected or even increased intake [1,2,4,18–20,29]. To further elucidate the importance of an ''alcohol history'' in NPY's suppression of ethanol intake, the effect of direct administration of NPY into the ventricles of rats with or without a history of ethanol vapor exposure was examined [35]. Here, the effects of NPY on alcohol intake were measured using animals in which dependence and high alcohol preference was induced using 8 weeks exposure to intermittent ethanol vapor (14 h on/10 h off per day; target BAL 200 mg%). This exposure models chronic alcohol consumption, and leads to long-term changes in neurochemistry as well as increases in alcohol intake [25,26]. The exposure of animals to ethanol vapor significantly elevated their baseline alcohol intake and, using this model, NPY was shown to significantly suppress alcohol intake in exposed animals as compared to saline treated controls. Notably, consumption was reduced back to but not below pre-vapor exposure levels [35]. In non vapor-exposed subjects, NPY icv had no effect on ethanol intake.

A second study was designed to determine whether NPY differentially alters ethanol-associated appetitive behavior (i.e., lever pressing) or ethanol consumption in Wistar rats with a history of ethanol vapor exposure. Rats were first trained to self-administer 10% ethanol in a paradigm that provided 25 min of free access to 10% ethanol after completing a 20-lever press response requirement (RR20) and then exposed for a 9-week period to intermittent ethanol vapor. Self-administration sessions were reinstituted after vapor exposure, and a fixed time (FT) schedule of 10% ethanol access was used to assess the effects of ethanol exposure and NPY on lever pressing and drinking behavior. Here, the number of lever–responses was measured for 10 min after which access to the ethanol solution was given regardless of the number of responses. Ethanol vapor exposure did not alter patterns of lever pressing under the RR20 schedule, but lever presses emitted under the FT schedule were reduced after ethanol vapor exposure, while ethanol intake was significantly increased. This may reflect a differential effect of ethanol exposure on appetitive and consummatory behavior, respectively, and supports the hypothesis that these two behaviors are regulated by different neurobiological systems. NPY significantly reduced ethanol intake but did not significantly reduce lever pressing under the FT schedule. Taken together, these data suggest that chronic ethanol exposure increases ethanol intake without clearly enhancing its reinforcing value [36]. Further studies are required to elucidate the level of ethanol exposure needed to induce not only an increase in alcohol intake but also an increased reward value of ethanol. It