European Neuropsychopharmacology (2006) 16, 272–280

www.elsevier.com/locate/euroneuro

Allopregnanolone produces hyperphagia by reducing neophobia without altering food palatability☆

Melissa A. Fudge*, **Martin Kavaliers** [1], **Klaus-Peter Ossenkopp** [1]

Neuroscience Program and Department of Psychology, Room 7418 Social Science Center, The University of Western Ontario, London, Ontario, Canada N6A 5C2

Received 4 May 2005; received in revised form 16 June 2005; accepted 9 August 2005

KEYWORDS
Anxiety;
Appetitive behaviors;
Consummatory behaviors;
Hyperphagia;
Drinking behavior;
Neurosteroid

Abstract The neurosteroid allopregnanolone may increase feeding by altering food palatability; however, it may also increase feeding by reducing anxiety (neophobia). Moreover, it is unclear whether this induced hyperphagia is selective to safe, palatable foods only. Male rats were injected with allopregnanolone 20 min prior to behavioral testing. The taste reactivity test was used to examine possible shifts in the palatability of a 0.3 M sucrose solution. A lickometer was used to monitor intake and licking of either a sucrose or sucrose–quinine solution. Sucrose palatability was not enhanced; however, allopregnanolone significantly increased sucrose intake and licking on Test Day 1 when the solution was novel, but not on Test Day 2 when the solution was familiar. Sucrose–quinine intake was not enhanced. Allopregnanolone-induced hyperphagia is not a result of altered sucrose palatability, but rather reflects a reduction in the neophobia elicited by a novel solution; an effect that further seems to be selective to safe, palatable foods.

1. Introduction

The potential clinical uses of the neurosteroid and progesterone metabolite allopregnanolone (5α-pregnan-3α-ol-20-one) have focused on anxiety disorders. Fluctuations in allopregnanolone have been reported in anxiety disorders such as panic disorders, premenstrual dysphoric disorder (PMDD) and depression (refer to Rupprecht, 2003 for a review of clinical findings). In addition to its roles in anxiety, allopregnanolone has been implicated in a variety of other behavioral processes. It has been shown to produce anesthetic, anticonvulsant, and hypnotic/sedative effects (refer to Smith, 2002 for review). Results of several previous studies have also demonstrated that allopregnanolone produces hyperphagic effects. Allopregnanolone was shown to reliably increase food consumption in non-food deprived male rats (Chen et al., 1996), deprived male and female rats

☆ This research was supported by Natural Sciences and Engineering Research Council of Canada (NSERC) grants to Martin Kavaliers and Klaus-Peter Ossenkopp. Melissa Fudge was supported by an Ontario Graduate Scholarship.
* Corresponding author. Tel.: +1 519 6612111x81214; fax: +1 519 661 3961.
E-mail address: mfudge@uwo.ca (M.A. Fudge).
[1] Tel.: +1 519 6612111x81214; fax: +1 519 661 3961.

0924-977X/$ - see front matter © 2005 Elsevier B.V. and ECNP. All rights reserved.
doi:10.1016/j.euroneuro.2005.08.002

(Higgs and Cooper, 1998; Reddy and Kulkarni, 1999), as well as deprived male mice (Reddy and Kulkarni, 1998; Sinnott et al., 2002). However, unlike allopregnanolone's anxiolytic properties, little is known about which aspects of feeding are altered by allopregnanolone to result in an increase in overall food consumption.

The act of feeding has previously been described as a two-component process consisting of an appetitive and a consummatory component (Craig, 1918; Cross-Mellor et al., 2003). Appetitive behaviors are goal-oriented behaviors that promote the foraging for food to reduce an energy deficit. These behaviors can consist of food recognition and approaches, as well as other behaviors that lead to the consumption of food. Consummatory behaviors, such as licking, chewing and swallowing, act to promote the ingestion of food and are elicited once a food substance has entered the mouth. Although these two components work in tandem to initiate and facilitate food consumption, there is evidence that these two components may be independently regulated or altered (Cross-Mellor et al., 2004). To understand the behavioral mechanisms involved in mediating allopregnanolone-induced hyperphagia, an examination of the effects of allopregnanolone on both of these components of feeding is necessary.

The taste reactivity test, developed by Grill and Norgren in 1978, is a measure of palatability and records orofacial and somatic behaviors in reaction to an intraoral infusion of a tastant directly into the mouth. As the intraoral infusion is a forced exposure procedure, the appetitive component of feeding is eliminated from the behavioral measures. Thus, the taste reactivity test provides a direct measure of the consummatory component of feeding only. The effects of allopregnanolone on food palatability have not been reported using the taste reactivity test; however, other GABA-A modulators, such as benzodiazepines, have been examined. Although it was originally suggested that benzodiazepines increase food intake by reducing anxiety, the hyperphagic and anixiolytic properties of benzodiazepines have been clearly dissociated (Cooper, 1980). Further studies using the taste reactivity test have instead shown that these GABA-A modulators alter food intake by enhancing palatability (Berridge and Treit, 1986; Treit et al., 1987; Parker, 1991, 1995). This suggests that benzodiazepines increase feeding by enhancing ingestive consummatory behaviors. As both benzodiazepines and allopregnanolone act as modulators at the GABA-A receptor and have a similar behavioral profile, the results of these taste reactivity studies suggest that it is possible that allopregnanolone could also increase food intake by altering ingestive consummatory behaviors.

In addition to altering the consummatory component of feeding, it is possible that allopregnanolone could alter the appetitive component of feeding as well. Allopregnanolone could directly alter appetitive behaviours, or it could alter other factors, such as anxiety, which may well alter these behaviours indirectly. One hypothesis that has been suggested is that the neurosteroid allopregnanolone may influence appetitive behaviors by reducing the anxiety associated with exposure to novel foods (neophobia) (Higgs and Cooper, 1998). In food intake situations, neophobia causes a reduction in the consumption of novel foods until further experience with the food is acquired. This process is very adaptive for non-emetic species such as rats (Hatcher, 1924). Once a food toxin has been ingested by a rat, it cannot be eliminated by vomiting. Therefore, an initial limitation of the intake of novel food items is highly advantageous as it reduces the amount of toxins that may potentially be ingested. To date, conflicting evidence exits on the role that anxiety/neophobia may play in allopregnanolone-induced hyperphagia. Chen and colleagues (1996) reported an increase in the consumption of a familiar sweetened mash in non-deprived male rats after the administration of allopregnanolone. Reddy and Kulkarni (1998) also reported dose-dependent hyperphagic effects produced by allopregnanolone using a familiar test diet. These results suggest that allopregnanolone-induced hyperphagia is not a secondary consequence of anxiety reduction as the animals were habituated to the diets prior to testing. Contrary to this, Higgs and Cooper (1998) were unable to replicate these hyperphagic effects in food-deprived male rats when measuring intake and licking of a variety of familiar sucrose solutions using the same 108 contact lick analysis system used in the present study. Intake of a mash diet was also not altered. However, they were successful at showing that pregnanolone (3α-hydroxy-5ß-pregnan-20-one), another neurosteroid and progesterone metabolite, inhibits the suppression of intake induced by neophobia by reducing anxiety, as pregnanolone treated rats spent more time eating novel foods.

The anxiolytic effects of allopregnanolone have been well characterized in a variety of behavioral tests. Allopregnanolone has been shown to reduce anxiety in the elevated plus maze (Rodgers and Johnson, 1998), light/dark test (Wieland et al., 1991), mirrored chamber test (Reddy and Kulkarni, 1997) and Geller—Seifter test (Wieland et al., 1995; Gulinello et al., 2003). However, behavioral studies, which compared allopregnanolone- and pregnanolone-induced anxiolytic effects, have found that pregnanolone is a more potent anxiolytic agent than allopregnanolone (Wieland et al., 1995). As such, the apparent involvement of anxiety reduction in the effects of pregnanolone on feeding (Higgs and Cooper, 1998) should not be directly extrapolated to allopregnanolone. Thus, a systemic investigation of the influence of allopregnanolone's anxiolytic effects on food consumption is needed.

The present experiments evaluated the impact of allopregnanolone on consummatory behaviors using the taste reactivity test (Experiment 1), as well as the potential mediating role of anxiety in allopregnanolone-induced hyperphagia using a one-bottle lickometer test (Experiment 2). The lickometer test provides a microstructural analysis of intake patterns by monitoring licking and allows for a greater understanding of the relative contribution of appetitive and consummatory behaviors to feeding. It was hypothesized that allopregnanolone would significantly increase consummatory behaviors in the taste reactivity test, consistent with research on benzodiazepines that also induced hyperphagia by modulating GABA-A receptors (Berridge and Treit, 1986; Treit et al., 1987; Parker, 1991, 1995). However, as was previously shown with another neurosteroid, pregnanolone, it was also hypothesized that allopregnanolone would significantly increase sucrose intake and licking by reducing anxiety, thus inhibiting the novelty-induced suppression of intake known as food neophobia.