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Cessation of alcohol consumption decreases rate of nicotine metabolism in male alcohol-dependent smokers

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ABSTRACT

Background: Rate of nicotine metabolism is an important factor influencing cigarette smoking behavior, dependence, and efficacy of nicotine replacement therapy. The current study examined the hypothesis that chronic alcohol abuse can accelerate the rate of nicotine metabolism. Nicotine metabolite ratio (NMR, a biomarker for rate of nicotine metabolism) and patterns of nicotine metabolites were assessed at three time points after alcohol cessation.

Methods: Participants were 22 Caucasian men randomly selected from a sample of 165 smokers entering a 7-week alcohol dependence treatment program in Poland. Data were collected at three time points: baseline (week 1, after acute alcohol detoxification), week 4, and week 7. Urine was analyzed for nicotine and metabolites to determine the nicotine metabolite ratio (NMR, a biomarker for rate of nicotine metabolism), and total nicotine equivalents (TNE, a biomarker for total daily nicotine exposure).

Results and conclusions: There was a significant decrease in urine NMR over the 7 weeks after alcohol abstinence (F(2,42) = 18.83, p < 0.001), indicating a decrease in rate of nicotine metabolism. On average NMR decreased 50.0% from baseline to week 7 (9.6 ± 1.3 vs 4.1 ± 0.6). There was no change in urine TNE across the three sessions, indicating no change daily nicotine intake. The results support the idea that chronic alcohol abuse may increase the rate of nicotine metabolism, which then decreases over time after alcohol cessation. This information may help to inform future smoking cessation interventions in this population.

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1. Introduction

Cigarette smoking and excessive alcohol consumption remain two of the leading preventable causes of premature death in the U.S. and around the world (Danaei et al., 2009). These are highly co-morbid behaviors and the prevalence of cigarette smoking in individuals with alcohol use disorders is high (see McKee and Weinberger, 2013 for review). Results from a national sample found the prevalence of any alcohol use disorders was higher among individuals with nicotine dependence compared to the overall population (22.8% vs 8.5%; Grant et al., 2004); and around half of all adults in the US with an alcohol use disorder also smoke cigarettes (McKee and Weinberger, 2013). Individuals with alcohol use disorders have also been found to be heavier smokers, report greater nicotine dependence, and have poorer smoking cessation rates (Burling et al., 1997; Cook et al., 2012; Friend and Pagano, 2005; Keenan et al., 1990; Hughes and Kalman, 2006; Hurt et al., 1995; John et al., 2003a; Marks et al., 1997; York and Hirsch, 1995).

Underlying factors that contribute to the differences in prevalence of cigarette smoking and nicotine dependence among individuals with alcohol use disorders remain unclear. Research
has largely focused on the hypothesis that nicotine and alcohol in combination may have combined pharmacological effects that support their co-use (e.g., increased reward and/or decreased withdrawal/aversive effects). An additional mechanism that could contribute to this difference in cigarette smoking behavior and dependence in this population is a change in the pharmacokinetics of nicotine induced by chronic alcohol consumption.

Nicotine is primarily metabolized into cotinine by the liver enzyme CYP2A6 (C-oxidation), which accounts for approximately 75% of nicotine metabolism (Benowitz et al., 2009). Cotinine is further metabolized to trans-3'-hydroxycotinine (3HC) in a process mediated exclusively or nearly exclusively by the same enzyme, CYP2A6. The ratio of 3HC/cotinine, termed the nicotine metabolite ratio (NMR) is a validated biomarker for CYP2A6 activity and the rate of nicotine metabolism (Dempsey et al., 2004). A higher NMR indicates greater CYP2A6 enzyme activity and faster rate of nicotine metabolism.

In addition to cotinine and 3HC, nicotine is metabolized to a number of other metabolites via the CYP2A6 and other metabolic pathways (see Benowitz et al., 2009 for review). In the current study we also assessed a number of different metabolites of nicotine in addition to products from the C-oxidation pathway. For example nicotine is also metabolized by glucuronidation (primarily by UDP glucuronosyltransferase 2 family, polypeptide B10; UGT2B10) and N-oxidation (by flavin containing monoxygenase 3; FMO3), although these pathways contribute less to the overall metabolism of nicotine compared to CYP2A6 (Hukkanen et al., 2005). If metabolism of nicotine via the C-oxidation pathway is slower, higher levels of non-C-oxidation products (e.g., nicotine glucuronide and nicotine-N-oxide) would be expected.

A faster rate of nicotine metabolism (greater CYP2A6 enzyme activity) was previously found to be associated with smoking more cigarettes per day (Benowitz et al., 2003; Strasser et al., 2011; Tanner et al., 2015), greater nicotine withdrawal symptoms (Rubinstein et al., 2008; Sofuoglu et al., 2012), and decreased efficacy of nicotine replacement therapy (NRT) for smoking cessation (Lerman et al., 2006, 2015). Tobacco use characteristics associated with faster rate of nicotine metabolism are similar to what has been found in individuals with alcohol use disorders, as previously discussed. Both genetic (Ray et al., 2009) and environmental factors have been found to influence CYP2A6 enzyme activity. For example estrogen (Benowitz et al., 2006; Dempsey et al., 2002), and certain medications such as phenobarbital (Benowitz et al., 2009) and rifampicin (Xia et al., 2002) have been found to induce CYP2A6 enzyme activity, resulting in accelerated rate of nicotine metabolism.

Previous research suggests that chronic alcohol may induce CYP2A6 enzyme activity. Protein levels of CYP2A6 were found to be higher among patients who abuse alcohol (Niemela et al., 2000) and alcohol was found to induce CYP2A6 activity in the U937 macrophage cell line (Jin et al., 2011, 2012). In mice chronic alcohol consumption induced CYP2A5, the mouse orthologue of human CYP2A6 (Lu et al., 2011, 2012). The current study examined the hypothesis that chronic alcohol abuse accelerates the rate of nicotine metabolism and is associated with higher NMR and altered patterns of nicotine metabolism. We examined this hypothesis by looking at reversal of postulated metabolic induction after cessation of alcohol abuse, testing subjects at three time points over the course of 7 weeks of inpatient treatment for alcohol dependence. It was hypothesized that rate of nicotine metabolism assessed by NMR would decrease over the 7 weeks of alcohol abstinence, reflecting normalization after prior enzyme induction.

Total Nicotine Equivalents (TNE), the molar sum of nicotine and its metabolites measured in urine, is a highly reliable biomarker of total nicotine exposure (Scherer et al., 2007) that is unaffected by differences in CYP2A6 enzyme activity (Benowitz et al., 2010; Derby et al., 2008; Feng et al., 2007). TNE was used to determine if there was a change in nicotine exposure at the three assessments after alcohol cessation. In addition, biomarkers of liver function were also assessed to verify subjects did not have severe liver function impairments and to verify that the expected decrease in these liver function metabolites occurred after cessation of alcohol.

Understanding changes in nicotine metabolism associated with chronic alcohol abuse and recovery (during alcohol abstinence) could have important implications for understanding smoking behavior and improving smoking cessation interventions for current and former heavy alcohol drinkers.

2. Methods

2.1. Setting

The study was conducted from September 2011 to May 2012 at the Center for Addiction Treatment (Ośrodek Terapii Uzależnień, OTU), an inpatient program dedicated to the treatment of alcohol dependence located in Parzynowiec, Poland. The center treats approximately 1200 individuals per year for alcohol dependence with an average treatment duration per patient of 8 weeks. Patients entering the program were first treated for acute alcohol withdrawal for up to 2 weeks in an alcohol detoxification program. During detoxification, patients were administered benzodiazepines as needed, titrated down over subsequent days. Only intoxicated individuals or those with acute withdrawal symptoms were admitted to the alcohol detoxification program. Once patients were stabilized they entered a 7 week inpatient treatment program for alcohol dependence. The 7 week alcohol treatment program consisted of only psychotherapy. No pharmacotherapy was administered for alcohol dependence during the 7 week treatment program. Breath alcohol was monitored daily, up to 2 times/day. Any individual testing positive for alcohol was discharged and removed from the treatment program. At the end of the 7 week program patients were given the option to stay longer if needed. Inpatients were free to smoke cigarettes outside of the facility during their stay at the OTU.

The current study was approved by the Institutional Review Board of the Medical University of Silesia in Katowice Poland and conducted according to the Declaration of Helsinki, the European Guidelines on Good Clinical Practice, and relevant national and regional authority requirements and ethics committees. The current study was a secondary analysis of the dataset.

2.2. Participants

Men and women from the OTU alcohol addiction treatment center were recruited before entering the 7 week treatment program (after detoxification) for a study to examine the effects of vitamin supplementation during treatment of alcohol dependence. Inclusion criterion for the current analyses were: age 30–60, a diagnosis of alcohol dependence based on the ICD F10.2 criteria (WHO, 2010), and self-reported daily smoking for at least 5 years. Smoking status was self-reported and verified with a Fagerstrom Test for Cigarette Dependence (FTCD) score of 3 or greater, and expired carbon monoxide (CO) of 5 ppm or greater. Exclusion criteria were: a diagnosis of liver cirrhosis or kidney disease, recent myocardial infarction, high blood pressure, cancer diagnosis, pregnancy, diagnosis of major psychiatric disorder, and those taking inhibitors of renin-angiotensin system (RAS), statins, hormone replacement therapy (including estrogen and progesterone), aspirin, and erythropoetin (EPO). Participants were also excluded if they reported taking any vitamin supplements in the prior 2 months before entering the OTU program.
A total of 318 participants were screened for eligibility and 270 consented; 165 smokers completed all three sessions and were used in the current analyses. Nicotine biomarkers were assessed in 22 participants randomly selected from male smokers who completed all three assessments. Urine samples were randomly selected in Poland and shipped to the United States for analysis. Only a subset of the sample was analyzed for nicotine metabolites as it would have been cost prohibitive to analyze the full sample. Only male participants were included in this analysis as the overall sample was 83% male, and there are known sex differences in the metabolism of nicotine (see Benowitz et al., 2009 for review) that could complicate interpreting the effects of alcohol cessation on rate of nicotine metabolism.

2.3. Study protocol

All data collection occurred after cessation of alcohol consumption. The current study collected data at three time points: baseline (after remission of acute withdrawal symptoms from alcohol during the first week of the 7 week treatment program); week 4 (after completing 3 full weeks of treatment); and week 7 (after completing 6 full weeks of treatment). Assessment of nicotine withdrawal symptoms, smoking measures and urine samples were collected in the morning before the first cigarette of the day at each of the three time points. Patients were told not to smoke for at least 6 h (after midnight) the day before each assessment session which occurred between 6:00 and 7:00 AM Urine samples were frozen and stored at −20 °C. Urine samples were shipped frozen to the University of California, San Francisco for analysis of concentrations of nicotine and metabolites.

2.4. Measures

Demographic variables included age, sex, and body mass index (BMI). Usual cigarettes/day and cigarettes smoked during the past 24 h were self-reported. All individuals were diagnosed with alcohol dependence. Amount of alcohol consumption (e.g., usual drinks/day) was not assessed. Instead, years of heavy drinking before entering the treatment program was estimated by the participant. Participants entered screening after alcohol detoxification and the time since the last drink, before the baseline assessment session was calculated for each individual. Because there could be differences in duration of detoxification and assessments were performed after acute detoxification, there could be slight differences in number of days since individuals had last consumed alcohol. Expired breath carbon monoxide level (CO) and number of cigarettes smoked in the previous day were used to determine cigarette smoking behavior. Baseline nicotine dependence was assessed using the 7-item version of the Fagerstrom Test for Cigarette Dependence (FTCD; Heatherton et al., 1991).

2.5. Analytical methods

Urine samples were analyzed using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) for concentrations of cotinine, nicotine, trans-3’-hydroxycotinine (3HC), nicotine N'-oxide (NNO), cotinine N'-oxide (CNO), nornicotine (NNIC), norcotinine (NCOT) as previously described (Benowitz et al., 2010; Jacob et al., 2011). Samples were assayed with and without enzymatic deconjugation, and the differences between assays taken to be the conjugated metabolite concentration, as described previously. Urine creatinine was measured by LC–MS/MS with a limit quantitation of 0.05 mg/mL, using a method developed at the Clinical Pharmacology Research Laboratories at the University of California, San Francisco. Plasma levels of liver function enzymes aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyl transpeptidase (GGTP) were measured at the OTU in-house clinical laboratory in Poland.

2.6. Data analysis

NMR was calculated as the ratio of total 3HC over free cotinine [(free 3HC + 3HC glucuronide)/free cotinine]. This calculation provides the best estimate of CYP2A6 activity as it includes all cotinine that is not metabolized via glucuronidation (free cotinine), which is the precursor chemical, while accounting for all 3HC metabolized via the C-oxidation pathway (free 3HC + glucuronide 3HC), which is the product of CYP2A6 metabolism.

TNE was used a measure of total nicotine intake. TNE was used instead of cotinine because cotinine levels with a given level of nicotine intake are influenced by CYP2A6 enzyme activity (Zhu et al., 2013). Using cotinine as a biomarker of daily nicotine intake underestimates daily exposure in individuals with high CYP2A6 enzyme activity. TNE as a measure of daily nicotine intake is independent of individual differences in patterns of nicotine metabolism (Benowitz et al., 2010; Zhu et al., 2013). TNE was calculated as the molar sum of urine nicotine, and nicotine metabolites (cotinine, 3HC, NNO, CNO, NNIC, NCOT and their glucuronide metabolites). Nicotine biomarkers in urine and TNE were corrected for creatinine values. In addition, we examined the molar sum of all metabolites formed by C-oxidation (cotinine + 3HC + their respective glucuronides, cotinine N-oxide, nornicotine, and norcotinine) and the sum of all metabolites generated via pathways other than by C-oxidation (nicotine + nicotine glucuronide, and nicotine N-oxide) as a fraction of the total of all nicotine and metabolites excreted in urine. To examine minor pathways of nicotine metabolism we also computed urine ratios of nicotine glucuronide/nicotine, cotinine glucuronide/cotinine, 3HC glucuronide/3HC and nicotine N-oxide/nicotine.

For each measure, data from the three assessment time points were analyzed by ANOVA with repeated measures (RM-ANOVA). The current research was a secondary analysis of a vitamin supplementation study (participants received either vitamin [B6, B12 and Folic acid] or placebo). We are aware of no evidence that supplementation with any of these vitamins affects CYP2A6 activity or alters the rate of nicotine metabolism. Half of the sample analyzed for nicotine metabolites were from participants that received the vitamin supplementation and half were from the placebo group. Initial analyses included treatment condition (vitamin supplementation or placebo) in the model. Because there was no significant difference on the effects of alcohol abstinence on rate of nicotine metabolism between the vitamin and placebo treated participants, all analyses are presented collapsed on treatment condition. Significant RM-ANOVAs were interpreted using pairwise comparisons with Bonferroni corrections. Effects were considered significant at an alpha level of 0.05 or less. Statistical analyses were performed using SPSS 22 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Baseline characteristics

The baseline demographic, smoking, and alcohol drinking variables for the entire group of male and female smokers who completed the study (n = 165) are shown in Table 1. As discussed in methods, 22 male individuals were randomly selected for analysis of nicotine metabolites. Shown in Table 1 is a comparison of the subsample that was included in the metabolite assay compared to the overall sample population. The subsample and overall sample were comparable with the exception of a slightly higher average
3.2. Smoking behavior over the course of treatment for alcohol dependence

For the full sample, there was a slight but significant increase in the number of self-reported past day cigarettes smoked ($F_{(2,414)} = 7.34$, $p = 0.001$) at week 4 ($17.7 \pm 0.6$) and week 7 ($18.0 \pm 0.5$), compared to baseline ($16.5 \pm 0.6$). However, there was no significant change in smoking in the subsample (Fig. 1A). There was no significant change in expired breath CO level between the 3 assessments in either the full sample or the subsample (fig. 1B). There was also no significant difference in urine TNE over the three sessions assessed in the subsample (fig. 1C), indicating that there was no change in total nicotine exposure at each of the three assessments over 7 weeks of alcohol abstinence.

3.3. Changes in nicotine metabolism over 7 weeks of alcohol abstinence

Cessation of alcohol consumption resulted in a significant change in nicotine metabolites measured in urine over the 7 weeks of abstinence from alcohol (Table 2). Higher levels of urine cotinine were found on week 4 and 7 compared to baseline as well as lower urine 3HC levels on week 7 compared to baseline ($F_{(2,42)} = 5.83$, $p = 0.006$). NMR decreased significantly (Fig. 1A) over the 7 weeks of alcohol cessation ($F_{(2,42)} = 18.83$, $p < 0.001$). Overall NMR decreased 50.0% from baseline to week 7. A full profile of nicotine metabolites in urine at baseline and at week 7 is presented in Fig. 2. There was a 12.3% decrease in nicotine C-oxidation products, and an 88.5% increase in non-C-oxidation products found in urine comparing baseline to week 7 (Fig. 2). No significant changes were observed in urine ratios of nicotine glucuronide/nicotine, cotinine glucuronide/cotinine, 3HC glucuronide/3HC or nicotine N-oxide/nicotine.

![Graphs showing changes in tobacco use and nicotine metabolism over 7 weeks of abstinence.](image-url)
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was found to induce CYP2A6 activity in the U937 macrophage cell line (Jin et al., 2011, 2012). This finding is consistent with work in mice showing that chronic alcohol consumption induced CYP2A5 (Lu et al., 2011, 2012), the mouse orthologue of human CYP2A6. Together these results suggest that chronic heavy alcohol consumption may lead to an increase in the rate of nicotine metabolism, which recovers with cessation of alcohol consumption (Fig. 3).

It was previously reported that alcohol use was associated with higher NMR levels among individuals who drank <25 drinks/week (Chenoweth et al., 2014). This finding suggests the idea that alcohol consumption may be associated with more rapid nicotine metabolism in non-alcohol-dependent individuals. However, not all studies have found this relationship (Ferguson et al., 2012; Mwenifumbo et al., 2007). These inconsistent findings highlight the need to better characterize the relationship between amount, frequency, and duration of alcohol consumption in relation to the induction of nicotine metabolism.

An important aspect of this work was characterizing the change in the profile of nicotine metabolites from baseline to week 7 (Fig. 2). Overall we found a decrease in excretion of C-oxidation products and an increase in non-C-oxidation pathway products comparing week 1 to week 7 after alcohol abstinence. This shift in nicotine metabolite products is consistent with the interpretation that there was a decrease in CYP2A6 enzymatic activity at week 7 compared to baseline. Alcohol has also been found to induce the cytochrome p450 enzyme CYP2B6 (Hesse et al., 2004), which may be a minor pathway of nicotine metabolism. However induction of CYP2B6 would not affect the metabolism of cotinine to 3HC, and thus would not alter the NMR, suggesting the observed effects were due to a change in CYP2A6 enzymatic activity. In addition, we considered the possibility that alcohol abuse might alter nicotine metabolism by other enzymatic pathways. Our finding that the ratios of nicotine glucuronides/total nicotine, cotinine glucuronides/total cotinine, 3HC glucuronides/total 3HC, and NNO/total nicotine, did not significantly change during alcohol abstinence indicates that changes in minor nicotine pathways were not a significant factor influencing the nicotine metabolism or the observed changes in NMR.

The implications of our study are as follows. Lower smoking cessation rates are found in alcohol-dependent individuals, but not in former alcoholics (See Hughes and Kalman, 2006 for review). Higher NMR has been found to be associated with lower smoking cessation outcomes using nicotine replacement therapy (NRT; Lerman et al., 2006, 2015). Chronic heavy alcohol consumption may lead to an increase in the rate of nicotine metabolism, which could be one contributing factor to the poor smoking cessation rates in this population. Results from the current study suggest a normalization of the rate of nicotine metabolism had likely occurred by week 4 after alcohol cessation, as NMRs at week 4 were comparable to what has been measured in the general population (Benowitz et al., 2003). This could have implications for the timing or choice of smoking cessation treatments in recovering alcoholics. Future research should evaluate if NRT may be more effective as a smoking cessation intervention after a period of abstinence from heavy alcohol consumption or if individuals who are alcohol-dependent or heavy drinkers may require higher doses of nicotine replacement therapy or non-nicotine medications (such as varenicline or bupropion) for optimal smoking cessation efficacy.

Another implication of this work is that cotinine levels were significantly higher at 4 and 7 weeks after cessation of alcohol compared to the week 1 baseline, with no change in total nicotine exposure. Cotinine is often used as a biomarker for cigarette smoking. If chronic heavy drinking results in an induction of CYP2A6 metabolism, using cotinine as a biomarker of cigarette smoking would result in an underestimation of cigarette smoking in these individuals (Zhu et al., 2013). This has important implications for interpreting studies using cotinine as a biomarker tobacco exposure in this population.

Although there was a small but significant increase in self-reported number of cigarettes smoked for the full sample, there was no significant change in the subsample in which nicotine metabolites were assessed. In addition, there was no change in total nicotine exposure (TNE) or expired CO over the three assessment periods after alcohol cessation, indicating that nicotine or tobacco smoke intake did not change with the decrease in rate of nicotine metabolism. One might expect that as the rate of nicotine metabolism decreases, smokers would smoke fewer cigarettes and take in less nicotine per day, which was not observed. A lack of change, an increase, and a decrease in CPD have all been reported in individuals during treatment for alcohol dependence (Aubin et al., 2013). There are a number of other factors that influence smoking behavior in this population. Perhaps the effect of metabolic rate on smoking behavior would be observed over a longer period of time or when patients left the treatment facility.

Chronic heavy alcohol consumption is known to result in elevated levels of liver function biomarkers (ALT, AST, and GGTP). Results in the current study were consistent with a normalization of liver function biomarkers with cessation of alcohol consumption (Allen et al., 2001). These results suggest that the change in rate of nicotine metabolism corresponded with a normalization of liver function biomarkers seen at week 4 and week 7 compared to baseline. Minor elevations in liver enzymes are not likely to be causally associated with changes in drug metabolism. This correspondence was likely due to independent effects of alcohol cessation.

Consent for the current study occurred after participants were treated for acute alcohol withdrawal and the baseline sample occurred during the first week of alcohol abstinence. It is possible that the rate of nicotine metabolism would have been different when participants are actively drinking alcohol. For some drugs, acute alcohol consumption inhibits metabolism, while in the absence of alcohol, drug metabolism is accelerated due to underlying liver enzyme induction (Altomare et al., 1984). Also, in the first week of detoxification, before our baseline measurement, the rate of nicotine metabolism could have been even higher.

A limitation of the current study was that it is observational rather than experimental. All data was collected after alcohol abstinence. It would be difficult to prospectively study the effects of heavy alcohol use and withdrawal on nicotine metabolism for ethical reasons. An important future direction of this research is to examine rate of nicotine metabolism among current heavy drinkers and to better characterize the relationship between amount, frequency, and duration of alcohol consumption in relation to the induction of nicotine metabolism. Another limitation is that all of our subjects were male and Caucasian. Future research should examine if similar changes in nicotine metabolism are found in alcohol-dependent women smokers after cessation of alcohol consumption. In addition, there are known racial differences in rate of nicotine metabolism (Pérez-Stable et al., 1998; Shiffman et al.,...
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Contributions

N.R.G, N.L.B and M.L.G. wrote the manuscript. M.L.G and A.S designed the research. A.K.K., I.S.B., E.S.M., J.G. and M.L.G. performed the research and data collection. P.J. supervised the laboratory analyses of nicotine metabolites. N.R.G, N.L.B, and M.L.G. analyzed the data. All authors read and approved the final manuscript.

Conflict of interest

As received personal fees from the Smoking Institute in Poznan, Poland, and nonfinancial support from Chic Group LTD, a manufacturer of electronic cigarettes in Poland, outside of the submitted work. MLG received a research grant from Pfizer Inc., a manufacturer of smoking cessation medications. NLB serves as a paid consultant to pharmaceutical companies that are developing or that market smoking cessation medications. He also has been a paid expert witness in litigation against tobacco companies. All other authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2016.04.006.

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