

# Stroke Modifies Drug Consumption in Opium Addicts: Role of the Insula

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## ABSTRACT

**Introduction:** Addiction imposes a large medical, social and economic burden on societies. Currently, there is no effective treatment for addiction. Our struggle to decipher the different mechanisms involved in addiction requires a proper understanding of the brain regions which promote this devastating behavior. Previous studies have shown a pivotal role for insula in cigarette smoking. In this study we investigated the change in opium consumption after CVA.

**Methods:** This study took place in three referral academic hospitals affiliated to Tehran University of Medical Sciences. Patients who suffered a CVA and were addicted to opium were recruited during their hospitalization or visit to the neurology clinic in this study. Age, sex and the route and mean amount of opium use of each patient before CVA and 1, 3 and 6 months post-CVA was asked using a questionnaire. The patients were divided into three groups based on the location of brain ischemia (insula, basal ganglia and non-insula non-basal ganglia group).

**Results:** Seventy five percent of the patients with ischemia of the insula changed the route or amount of opium use after CVA and 37.5% of them stopped opium use after CVA. These values were significantly higher than patients with non-insula non-basal ganglia ischemia (p values 0.005 and 0.03 for change in route or amount and stopping opium use, respectively). This was not true in patients with ischemia of the basal ganglia. Younger patients were more likely to change the route or amount of opium use and stop opium use after CVA (p values 0.002 and 0.026, respectively).

**Discussion:** The results of the present study indicate a possible role for the insula in opium addiction, especially in younger individuals.

## Key Words:

Stroke,  
Addiction,  
Opium.

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### 1. Introduction

**O**pium contains morphine and codeine and its narcotic and analgesic properties are attributed to these compounds.(Reddy, Suresh, Jayashanker, Rao, & Sarin, 2003) It is a widely used addictive substance in Asian countries including Iran.(Mokri, 2002) Opium is recreationally used by inhalation, oral intake or enema.(Alemi, 1978; Paoli, Greenfield, Charles, & Reuter, 2009) Illicit drug abuse imposes a large social, economic and medical burden on the society.(Ghotbi & Tsukatani, 2007; Rehm et al., 2009)

Much endeavor has been devoted to unravel the mysteries of addictive behavior. Regarding this fact, a great focus has been placed on exploring different brain regions implicated in addiction. Studies on psychostimulants constitute the great proportion of research in this field.(Degoulet, Rostain, Abraini, & David, 2011; Veeneman, Broekhoven, Damsteegt, & Vanderschuren, 2011) However, a gap exists in the field of opiates.

Classically, the ventral tegmental area and nucleus accumbens (NAcc) have been considered to play the key role in addiction.(Bradberry & Roth, 1989; Nisell, Nomikos, & Svensson, 1994) However, more recent research revealed that these regions are not the sole promoters of addictive behavior. Apart from the NAcc, other constituents of the basal ganglia have also been suggested to have an important role in the formation of addictive behavior.(Everitt & Robbins, 2005) Lately, there has been a great focus on the insula as a probable neuroanatomical

substrate of addiction.(Naqvi & Bechara, 2009; Naqvi, Rudrauf, Damasio, & Bechara, 2007)

Studies on addicted patients who suffer from a cerebrovascular accident (CVA) can provide a better understanding of different brain regions involved in addiction. Naqvi et al. studied 69 cigarette smokers with CVA. Their findings implicated a pivotal role for the insula in addiction to cigarette. In the present study we assessed the change in amount of opium consumption by addicted individuals with CVA, with regard to the location of their ischemia.

### 2. Methods

This study was undertaken in three hospitals of Tehran University of Medical Sciences. Data were collected at neurology clinics. We interviewed patients who had been hospitalized during February 2009 to May 2011 with a diagnosis of ischemic CVA and had a previous history of opium consumption documented during their hospitalization period or their follow up visit to the hospital's neurology clinic. We only included patients with ischemic CVAs to insure that the investigated groups are as homogeneous as possible, and therefore, those with hemorrhagic CVAs were not studied. Only patients who had been using opium for a period of at least one year prior to CVA were included in the study. Patients with aphasia or amnesia, those with physical disability which hampered drug use (e.g. debilitating movement disorder and blindness) and those who were receiving methadone maintenance therapy were excluded. Written informed consents were obtained from patients who agreed to participate in the study. Participants were assured that

**Table 1.** Different anatomical regions in each group of CVA

Insula	Right or left insula ischemia
Basal Ganglia	periventricular , thalamus , basal ganglia and pons
	parietal lobe and basal ganglia
	lacunar
	head of caudate
Non Insular-non Basal Ganglia	lacunar ischemia of periventricular white matter , loop Myer , centrum semiovale
	left medullary infarction
	tempor-occipital
	temporal uncus
	frontal lobe and precentral gyrus
	temporo-parietal
	parieto-occipital
	hippocampus
	temporal, frontal, parietal lobes in cortical and white matter
pons , medulla and corona radiata	

the data would be kept confidential. This study was performed in accordance with the Declaration of Helsinki and it was also approved by the ethical review committee of Tehran University of Medical Sciences.

We used a checklist during the interviews. Sex, age at lesion onset, amount and route of opium consumption before CVA and at different time points after CVA (1, 3 and 6 months post-CVA) were documented. Since most of the patients referred to the neurology clinic about one month after discharge, they had to be contacted later to determine their opium consumption 3 and 6 months after CVA. At the end of the interview open questions were used to compare the financial status of the participants before and after CVA to rule out inability to afford opium as a reason for decrease in opium consumption. Brain MR Images and CT scans of the patients were obtained shortly after the initial interview (a little over a month after CVA). The images were examined by three different expert neuroradiologists to localize the site of the lesions. The neuroradiologists were unaware of the mean amount of opium used by the patients. We divided the patients into three groups based on the location of their lesions. These groups were the insula group, the basal ganglia group and the non-insula non-basal ganglia group.

The mean amount of opium consumption (grams per day) was calculated for each patient based on the data collected by the questionnaires. Patients were grouped based on the location of their lesions. SPSS version 13 (Chicago, IL, USA) was used to analyze the data. We used the Shapiro Wilk test to assess normality of the data. The Friedman's test was used to compare mean opium consumption before CVA and at different time points after CVA. We used a method described by Conover as the post hoc test for Friedman's test.(Conover, 1980) Mann Whitney U and Kruskal Wallis tests were used to compare mean amount of opium consumption and the percentage of reduction in opium use at different time points after CVA in different groups of patients. We used a binary logistic regression to investigate the presence of a relation between the location of brain lesions and cessation of opium consumption or change in route or mean amount of opium consumption after CVA. Age at lesion onset was entered as a covariable in this analysis.

### 3. Results

As mentioned earlier in the methods section, patients with post-CVA physical disabilities which hampered drug use were not included in the study. We interviewed 47 patients and all interviewed patients responded to all

**Table 2.** Amount of opium consumption before and after CVA in patients with insula and basal ganglia ischemia.

Anatomical location of stroke	Estimated amount of opium consumption (grams per day)			
	before CVA	1 month post-CVA	3 months post-CVA	6 months post-CVA
Insula	1.0	0.33	0.33	0.33
	0.33	0.33	0.33	0.33
	0.5	0.5	0.5	0.5
	1.5	0.33	0.33	0.33
	0.5	0.5	0.5	0.5
	0.33	0.0	0.0	0.0
	0.33	0.0	0.0	0.0
	0.5	0.0	0.0	0.0
Basal ganglia	1.5	1.5	1.5	1.5
	1.0	1.0	1.0	1.0
	3.0	0.75	0.75	1.0
	2.0	2.0	2.0	2.0
	1.5	1.0	1.0	1.0
	2.0	2.0	2.0	2.0
	0.33	0.0	0.0	0.0
	1.0	1.0	1.0	1.0
	0.5	0.0	0.0	0.0

questions. Two patients were excluded from the study to eliminate change in financial status after CVA as a confounding factor, since they stated that they lost their jobs after CVA. Another patient was excluded because of post-CVA blindness. The remaining patients were included in the study (40 males and 4 females). Their age ranged from 43 to 89 with a mean of 62 and a standard deviation of 9. The mean age of patients in the insula, basal ganglia and non-insula non-basal ganglia groups were  $61.5 \pm 1.6$ ,  $61.2 \pm 2.0$  and  $62.6 \pm 2.1$ , respectively, which were not significantly different from each other (data represented as mean  $\pm$  S.E.M.). Interview sessions were discussed and arranged with the patients during their first interview. All 44 patients were interviewed in determined dates to evaluate their drug consumption habit in 3 and 6 months post CVA. Subsequent interpretations of their MRI revealed anatomic location of lesion, summarized in table-1. None of the patients in this study referred to any rehabilitation centers.

Seven patients (15.9%) suffered an ischemia of the insula. Eight patients (18.2%) had an ischemia in basal ganglia, one patient (2.2%) with infarction in both insula and basal ganglia, data of whom are presented in table-2, and one patient (2.2%) with hippocampus injury. Twenty seven patients (61.4%) had brain ischemia involving other brain regions. The patient who suffered a hippocampus infarction was grouped along with patients of the non-insula non-basal ganglia group. This patient didn't change the amount or route of opium use after CVA.

Seventeen patients ( $38.6 \pm 7.2\%$ ) changed the amount or route of opium use after CVA. One of these patients had both an insular and a basal ganglia lesion. Five of them had an insular lesion without involvement of the basal ganglia and four of them had a basal ganglia lesion without involvement of the insula. The seven remaining patients who changed their route or amount of opium use

had lesions in brain regions other than the insula or basal ganglia. Mean age of patients who did not change the route or amount of drug use was  $66.1 \pm 1.7$ , while patients who changed the route or amount of drug use had a mean age of  $56.3 \pm 1.6$ . Patients with infarctions of the insula were more likely to change the amount or route of drug use after CVA (p value = 0.005, odds = 32.8). However, patients with lesions in the basal ganglia did not have a higher chance of changing the route or amount of opium use after CVA in comparison to patients of the non-insula non-basal ganglia group (p value = 0.096). In addition, older patients had a lower probability of changing the amount or route of drug use after CVA (p value = 0.002, odds = 0.80). Five out of six ( $83 \pm 16\%$ ) patients with ischemia in the right insula changed their route or amount of opium consumption. We excluded the 2 patients with ischemia in the left insula and repeated the same analysis. As before, right insular ischemia significantly affected change in route or amount of opium consumption (p value = 0.01, odds = 36.15).

Eight patients stopped opium use after CVA and remained abstinent up to 6 months post-CVA. One of them had ischemia in both insular and basal ganglia, two had an ischemia in the insula without involvement of the basal ganglia and two with ischemia in the basal ganglia without involvement of the insula. The mean age of patients who stopped opium use after CVA was  $55.9 \pm 2.4$  while mean age of those who did not stop opium use was  $63.7 \pm 1.5$ . Patients with ischemia in insula were more likely to stop opium consumption after CVA and remain abstinent in comparison to patients of the non-insula non-basal ganglia group (odds = 30.86, p value = 0.03). However, the analysis did not yield a significant p value when patients of the basal ganglia and the non-insula non-basal ganglia groups were compared (p value = 0.109). Age inversely correlated with the probability of stopping opium consumption (p value = 0.026, odds = 0.81). Three out of

**Table 3.** Comparison of the percentage of reduction in opium consumption in different groups (data are presented as mean  $\pm$  SEM).

Group	Percent of reduction in opium consumption 1 month post-CVA	Percent of reduction in opium consumption 3 month post-CVA	Percent of reduction in opium consumption 6 month post-CVA
Insula	$55.6 \pm 16.8$	$55.6 \pm 16.8$	$55.6 \pm 16.8$
Basal Ganglia	$34.2 \pm 14.9$	$34.2 \pm 14.9$	$33.3 \pm 14.7$
non-Insula non-Basal Ganglia	$12.5 \pm 5.4$	$14.3 \pm 5.8$	$14.9 \pm 5.8$
All Patients	$24.5 \pm 5.8$	$25.6 \pm 5.9$	$25.8 \pm 5.9$

six ( $50 \pm 22\%$ ) patients with ischemia in the right insula stopped opium use after CVA. The same analysis was repeated after excluding the two patients with ischemia in the left insula. As before, ischemia in the right insula was associated with stopping opium consumption after CVA ( $p$  value = 0.022, odds = 31.3).

The mean amount of opium used by the patients in different groups did not follow a normal distribution. The amount of opium use changed significantly after CVA in all three groups in our study ( $p$  values: 0.002, 0.012 and 0.002 for insula, basal ganglia and non-insula non-basal ganglia groups, respectively). The post hoc analysis revealed that mean opium consumption at 1, 3 and 6 months post CVA was significantly lower than mean opium consumption before CVA in all 3 groups of patients ( $p$  value < 0.05).

A Kruskal Wallis analysis revealed that the mean amount of opium use of patients of the insula, basal ganglia and non-insula non-basal ganglia groups were significantly different at all time points of the study ( $p$  values 0.03, 0.006, 0.006 and 0.008 for before CVA, 1 month post-CVA, 3 months post-CVA and 6 months post-CVA, respectively). Mann Whitney U test with a Bonferroni correction for multiple comparisons showed that patients with insular infarction used a significantly lower amount of opium before CVA, 1 month post-CVA, 3 months post-CVA and 6 months post-CVA in comparison to patients with non-insula non-basal ganglia infarctions ( $p$  values 0.033, 0.003, 0.003 and 0.003, respectively).

Since the mean amount of opium use before CVA differed between the three groups, we decided to compare the percentage of decrease in the amount of opium consumption between the groups instead of comparing the absolute amount of opium use at different time points between the groups (Table 3). The percentage of decrease in the amount of opium consumption in different groups was not normally distributed. Kruskal Wallis analysis revealed that there was a statistically significant difference between the percentage of decrease in the amount of opium consumption between the three groups ( $p$  values 0.033, 0.39 and 0.38 at 1, 3 and 6 months post-CVA, respectively). A Mann Whitney U test with a Bonferroni correction for multiple comparisons showed that patients with ischemia in insula had a higher percentage of reduction in opium use in comparison to patients with non-insula non-basal ganglia ischemia ( $p$  values 0.036, 0.039 and 0.036 at 1, 3 and 6 months post-CVA, respectively). However, this was not true for patients with ischemia in basal ganglia ( $p$  values 0.40, 0.45 and 0.52 at 1, 3 and 6 months post-CVA, respectively).

#### 4. Discussion

Results of this study show that patients with ischemia in the insula were more likely to decrease or stop opium consumption after CVA. The present study provides further evidence for the role of insula in addiction. Several lines of evidence support the fundamental role of the insula in addiction to various compounds. Naqvi et al. reported 69 cigarette smokers with lesions in different brain regions. In accordance with our study, they found that patients with insular injury (especially right insular injury) had a higher probability of stopping smoking in comparison to patients with lesions in other brain regions. (Naqvi, et al., 2007) Furthermore, it has been shown that inactivation of the insula by lidocaine disrupts amphetamine induced place preference in rats. (Contreras, Ceric, & Torrealba, 2007) Additionally, schizophrenics (a population prone to cigarette addiction) and cocaine abusers have a reduced insula grey matter. (Crespo-Facorro et al., 2000; Franklin et al., 2002) This implicates that insula dysfunction might predispose individuals to addiction. (Naqvi & Bechara, 2009) Naqvi and Bechara suggest that insula plays an essential role in addiction by providing conscious pleasure, causing cue-induced urges and biasing decision making processes towards drug use. (Naqvi & Bechara, 2010) Our study is the first to provide evidence for the role of insula in addiction to opiates.

Craig proposed that insula receives sensory inputs from various parts of the body which are relevant to maintaining homeostasis, e.g. pain, taste, palpation, heartbeat, temperature, visceral senses from the respiratory and GI tract. Craig referred to these sensory inputs as interoception. (Blomqvist, Zhang, & Craig, 2000; Craig, 2002, 2004) The interoceptive inputs to insula, give rise to conscious emotions, i.e. the knowledge of how we are feeling. Considering the foregoing facts, Naqvi explains that the interoceptive effects of drugs which depend on the drug-use ritual (snorting, smoking, injecting etc) are aversive in nature but become pleasurable when drug use is continued because of being associated with reward. Another way of saying this is that the addicted individual learns to enjoy the interoceptive effects of drugs whether or not they are accompanied by the drug. (Naqvi & Bechara, 2009)

According to Naqvi et al. patients who suffer CVA are more concerned about their health. Thus a great proportion of cigarette smokers in their study quit smoking after CVA, irrespective of the location of their brain lesions. (Naqvi, et al., 2007) This might explain why the mean amount of opium use decreased in all three groups of patients (insula, basal ganglia and non-insula non-basal

ganglia group) after CVA in our study. Indeed, previous studies have shown that onset of smoking-related diseases (e.g. myocardial infarction, CVA and etc.) greatly increases the likelihood of smoking cessation.(Twardella et al., 2006) Notwithstanding the foregoing, patients with insular ischemia had a significantly higher percentage of reduction in the amount of opium use in comparison to patients with non-insula non-basal ganglia infarctions at different time points after CVA, indicating a key role for the insula in opium addiction.

Among all the various brain systems implicated in addiction by far the most notorious is the mesolimbic dopaminergic system. The neurons of this system arise from the brainstem ventral tegmental area and have dopaminergic projections to the NAcc. Today there is a consensus that the motivation for continued use of nearly all drugs of abuse is caused, at least in part, by their ability to release dopamine from the mesolimbic system.(Everitt & Robbins, 2005; Naqvi & Bechara, 2009) Although addiction is initially a goal directed act, it ultimately evolves into a stimulus-response (habit) behavior.(Everitt & Robbins, 2005) The dorsolateral striatum is thought to be responsible in maintaining the drug seeking habit during prolonged periods of drug absence. (Vanderschuren, Di Ciano, & Everitt, 2005) These findings have led to the belief that the striatum, as a whole, participates in the initiation and persistence of addictive behavior.(Everitt & Robbins, 2005) To assess the role of the striatum in opium addiction we studied patients with infarctions involving the basal ganglia and found no association between ischemia in basal ganglia and cessation/reduction of opium use after CVA. Although there is the possibility that opium addiction is independent of the striatum, it is also possible that bilateral basal ganglia infarction is required to influence opium use. The finding that bilateral pharmacological inactivation of the dorsal striatum is required to abrogate drug seeking behavior supports this idea.(Vanderschuren, et al., 2005) Another explanation for such an unexpected result could be the small sample size in our study. Further studies are required to elucidate the role of the basal ganglia in opium addiction.

Apart from its role in the formation of new memories, the hippocampus has a part to play in addictive behavior. When an individual confronts a previously experienced context of drug consumption, glutaminergic hippocampal projections to the NAcc are activated. This activation reinforces drug seeking behavior.(Everitt & Robbins, 2005; Nestler, 2001) Since hippocampal injuries alter locomotor activity (Caine, Humby, Robbins, & Everitt, 2001) it is likely that these contextual memories control

the individual's motivation to seek drugs.(Everitt & Robbins, 2005) Previous studies emphasize on the role of the ventral hippocampus in addictive behavior.(Caine, et al., 2001) Only one patient had hippocampal infarction in our study. The amount of opium used by this patient did not change after CVA. This might be due to the location of the ischemia, since it involved only the posterior part of the hippocampus, sparing the ventral hippocampus.

Younger patients in our study were more likely to quit opium use after CVA. Although psychological motivations (i.e. holding addiction responsible for stroke in an early age and trying to avoid further drug use) could be an explanation for this finding, but this might also indicate that neural circuits of opium addiction change with aging. It has been shown that age affects mu-opioid receptor binding in many regions of the human brain. (Zubieta, Dannals, & Frost, 1999) Moreover, D2 dopamine receptors, which have been suggested to play a key role in formation of addictive behavior,(Noble, 2000) are reduced in older individuals.(Volkow et al., 1996) Contrary to opium addicts, younger cigarette smokers are less likely to quit smoking after CVA.(Bak et al., 2002) More research needs to be done to address this issue.

An unanticipated finding in our study was that individuals with ischemia in the insula consumed less opium before CVA and at different time points after CVA in comparison to individuals with non-insula non-basal ganglia ischemia. One explanation for this finding is that opium might make neurons of the insula more resilient against ischemia. A number of studies provide data in support of this assumption. It has been demonstrated that kappa opioid receptor agonists possess neuroprotective properties and decrease the infarction size in animal models of CVA. Interestingly, these opioid agonists do not cause cerebral blood flow alteration and probably act at the neuronal level. Moreover, this effect seems to be region specific, since it doesn't affect all brain regions. (Mackay, Kusumoto, Graham, & McCulloch, 1993) In another study, it was shown that endogenous opioids and exogenously administered morphine reduce the volume of infarction in an animal model of CVA.(Zhou et al., 2011) These findings might explain why patients who consumed higher amounts of opium were less likely to suffer insular infarctions. On the other hand, another explanation for this finding could be that individuals with more active insular cortices experience the same amount of desirable interoception with lower amounts of drugs. (Naqvi & Bechara, 2009) For this reason, these individuals routinely consume lower amounts of drugs than other addicts, yet they too experience the "high" feeling. Nevertheless, a more active insula might be more susceptible

to ischemic insults. (Saleh, Connell, Legge, & Cribb, 2004) More research needs to be done before claiming such assumptions.

One of the major shortcomings of our study is that we allocated all the patients with infarctions involving different parts of the basal ganglia into one single group. For instance, patients with strokes involving the amygdala were grouped along with those who had NAcc infarctions. Moreover, other locations which have been proposed to have a role in addiction, such as the orbitofrontal cortex, were not evaluated in our study.

In essence, the results of the present study are in support of previous studies suggesting a key role for the insula in addiction. In contrast to a previous study in cigarette smokers which reported that younger individuals are less likely to quit smoking after CVA, older patients in our study continued to use the same amount of opium after CVA. Additionally, patients with insular infarction in our study consumed less opium both before and after CVA.

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